Access DB# 66044

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Lotfi Thanh Examiner #: _____ Date: 5/6/02
Art Unit: 3763 Phone Number 305-0038 Serial Number: 09/205,251
Mail Box and Bldg/Room Location: CP2-3D07 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

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Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Controlled Release System for delivering therapeutic Agents into the Inner Ear

Inventors (please provide full names): Irving K. Arenberg, Michael H. Arenberg, Christine Lemke, John Berglund

Earliest Priority Filing Date: 12/4/98

***For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.**

Please search all commeraal database
See claims 1-6, 20-25
search for delivering agents to the
innerear thru round window, & membrane niche
using synthetic carrier

****

STAFF USE ONLY	Type of Search		Vendors and cost where applicable	
Searcher: Anne Hendrickson	NA Sequence (#)		STN	X
Searcher Phone #: 305-5934	AA Sequence (#)		Dialog	X
Searcher Location: EIC 3700	Structure (#)		Questel/Orbit	
Date Searcher Picked Up: 5/20/02	Bibliographic		Dr.Link	
Date Completed: 5/21/02	Litigation		Lexis/Nexis	
Searcher Prep & Review Time: 30min	Fulltext		Sequence Systems	
Clerical Prep Time: 240	Patent Family		WWW/Internet	X
Online Time: ~~240~~ min	Other		Other (specify)	

PTO-1590 (1-2000)

05-21-02

Re: 09/205,251 – Controlled Release System for delivering therapeutic agents into the Inner Ear

Examiner Thanh,

Attached are the results of my search of the nonpatent and foreign patent commercial databases. I have also enclosed references that I found on the Internet. Many of the pertinent references were published after the 1998 priority date. I have flagged references that I thought might be of interest. I have also enclosed info on the Silverstein Microwick for a sponge placed on the round window membrane.

Please let me know if you have any questions or need further assistance or explanation.

Thanks,

Anne Hendrickson
EIC3700
305-5934

On the Level

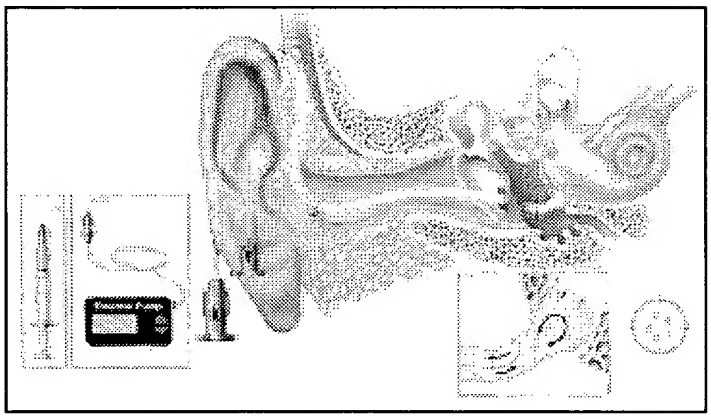
Quarterly Newsletter of the
Vestibular Disorders Association
Vol. 15, No. 4, Fall 1998

Invention May Improve Drug Delivery to the Inner Ear

By Jane S. Mahoney

A micro-catheter invented by a Colorado physician may be making life easier for some people with vestibular and cochlear disorders and for the physicians who treat them.

A catheter is a tubular device that allows passage of fluid from or into a body cavity. The micro-catheter devised by I. Kaufman Arenberg, M.D., at IntraEar, Inc., is meant to deliver doses of gentamicin or other medications to the inner ear with greater precision than may be possible by other methods.



Round Window μCath—Liquid flows between a syringe or pump and the round window niche via a flexible tube with a "shower head." The tube is divided in two by an internal wall that allows fluid to flow out as well as in. The inset at left shows both a syringe and an external pump. The inset at right shows the tube's dividing wall at the turn-around point near the round window. The circular inset depicts the "shower head."

Dr. Arenberg's Round WindowμCath (RWμCath) enables otolaryngologists and otologists to direct medications to the round window membrane between the middle ear and the inner ear. During an outpatient procedure, physicians can thread the RWμCath tube

(continued on page 3)

Inside this Issue

Intervention May Impr ve Drug Delivery *(continued from page 1)*

into the ear canal, through a small ear-drum puncture made by the physician, and into the round window niche. Once in place, the micro-catheter is connected to a pump or syringe. The tip of the catheter serves as a miniature shower head and releases a measured micro-dose of medication directly onto the round window membrane.

The RWμCath method of getting medications to the round window differs from the more common treatment strategy of using a hypodermic needle inserted through a small ear drum puncture into the middle ear space at a distance from the round window. Both methods rely on diffusion across the round window membrane to deliver medication from the middle ear to the inner ear. The main difference lies in the approach. Dr. Arenberg likens the transtympanic needle approach to a "shotgun from long range" and his RWμCath to a "rifle from close range." He describes the micro-catheter function as "bulls-eye targeting," a concept that first occurred to him while he was performing surgery.

Greater precision in round-window targeting is meant to control the dose actually reaching the inner ear. In the case of gentamicin sometimes used to destroy balance hair cells in someone with Meniere's disease, large doses can accidentally damage hearing. More controlled doses may selectively destroy balance hair cells while sparing the hearing. The object of destroying balance hair cells is to control or eliminate vertigo.

LCDR Michael Hoffer, M.D., leading a team at a Navy medical center in San Diego, performed the first treatment using the RWμCath. In July 1997, he administered low doses of gentamicin to a round window of someone with Meniere's disease, an inner ear disorder that can cause vertigo, hearing loss, tinnitus (ear ringing or noise), and sensations of ear fullness. In this and other cases, Dr. Hoffer has reported either significant or total elimination of vertigo, reduction in tinnitus and sensations of ear pressure, and no additional hearing loss in most of his patients, as well as some hearing improvement.

According to Dr. Arenberg, about 40 physicians in North America, Europe, Asia, and Australia use the RWμCath or a similar device called the E-Cath. The E-Cath is identical to the RWμCath except that it includes a platinum electrode for recording electrocochleograms (ECoGs). Both devices are distributed by IntraEAR, Inc., a company formerly called Neuro-Biometrix that Dr. Arenberg and sons Michael and Daniel founded in 1996.

As with all surgical treatments, some risk is involved. Possible adverse reactions or safety hazards associated with the microcatheters and listed in an IntraEAR document include middle-ear infection, middle-ear inflammation without infection, round window rupture, chronic perforation of the ear drum, and inadvertent dislodgement of the micro-catheter from the round window niche. ■

Vertigoheel *(continued from previous page)*

ultra-highly diluted and can be defined and studied by conventional medical methods, according to a news release from Heel, Inc.

How Vertigoheel works to control vertigo is not fully understood, investigators said.

Full prescribing information about Vertigoheel can be found on page 1187 of the *1998 Physicians' Desk Reference*.

Reprint requests for the journal article should be addressed to Michael Weiser, MBChB, Biologische Heilmittel Heel GmbH, Dr-Reckeweg-Strasse 2-4, D-76532, Baden-Baden, Germany (e-mail: weiser.michael@heel.de). ■

Summary

AUDIOLOGY-NEWSLETTER

3°, Winter 1996

Immunological Diseases of the Ear (Positano, Italy, 24-26 October, 1996)

Held in the splendid Hotel 'Le Agavi' in Positano, the Symposium on 'Immunological Diseases of the Ear' (24-26 October, 1996) was organized by the Center for Hearing and Deafness, University of Buffalo, USA, (Donald Henderson) and the Audiology and Otology Center, University of Bari, Italy, (Antonio Quaranta). The Scientific Program brought together leading experts in the field, who, with their experience, discussed the state of the art in the field of immunological diseases of the ear, before a specialized audience. The presented papers are to be published by the New York Academy of Sciences in a single volume later this year.

Middle Ear

Otitis media with effusion, which together with the acute, purulent form is one of the most common causes of childhood illness, does not derive from immuno-deficiency (humoral or cellular) but represents an active process (Van Cauwenberge) in which bacterial strains, isolated or in association (50% of cases) with virus (Fadden, Chonmaitree) are involved. Lymphatic tissue on the mucous membrane of the upper airways, adenoids and tonsils included, has defense potentials through **secretory antibodies**, produced by type B-lymphocytes. Secretory IgA have an important role in this process, while IgG appear when the mucous is not able to eliminate antigenic aggression (Brandtzaeg). The reduced production of secretory IgA is at the origin of otitis-proneness found in some children, and is often associated with an alteration in the local production of **cytokines** (Bernstein). Prellner has suggested that the origin of the tendency to suffer from recurrent acute otitis media could be a genetic defect with positivity of the antigens HLA-A2 and HLA-A3. The cellular events at the base of bone resorption and remodeling in chronic otitis media and cholesteatoma are reported by DiMunzio and Chloe. The latter has also underlined the primary role of the arachidonic acid metabolites in the regulation of complex bone modifications in the presence of cholosteatoma, suggesting that **bone resorption** due to activated osteoclastis is regulated by specific neuropeptides such as substance-P. Bellussi has pointed out how some forms of cholesteatoma can assume biological characteristics that allow auto-maintenance or recurrency in spite of complete eradication.

Middle Ear/Inner Ear Interactions

The **round window membrane** is one of the weakest parts between the middle and inner ear, and changes in its permeability can be the consequence of bacterial aggression, as occurs during chronic or acute purulent otitis (Hellstrom). The ultra-structural characteristics of the round window membrane are responsible for transferring aminoglycoside antibiotics, which can be introduced into the middle ear with therapeutic aims for the inner ear (Bagger-Sjöbäck). Juhn has noted that when one of the inflammatory

mediators released in the middle ear cavity during otitis media, **platelets activating factor** (PAF), is experimentally applied to the the round window membrane, an increase in the ABR threshold and a decrease of otoacoustic emissions occurs.

Inner Ear

The inner ear can no longer be considered as an immunologically privileged organ, from the immunitary point of view. Various experimental studies have shown that it is infact the site of local immunological activity, produced and regulated by the endolymphatic sac (Harris). The sac contains cellular elements, such as macrophages and lymphocytes, and there is a passage of immuno-competent cells from the systemic circulation into the inner ear (Ryan). Accordingly, its proximity to the petrous bone marrow plays an important role (Barbara). There are systemic autoimmune diseases which later during the course of the disease develop hearing loss (e.g. connective tissue diseases, vasculitis syndromes). But sensorineural hearing loss can also be the first symptom of a later fully developing systemic autoimmune disease (Arnold). Clinical observation is the first diagnostic selective criteria on, even though presentation can range from endolymphatic hydrops to bilateral sensorineural hearing loss, sudden or rapidly pogressive (Veldman). Audiometric findings can also be more carefully analyzed through the study of temporal integration, frequency selectivity, remote masking and acoustic otoemissions (Quaranta). Laboratory methodologies able to diagnose an immuno-mediated disease of the inner ear are based on the reaction of serum from patients against inner ear antigens, preferably human, sampled during translabyrinthine surgery (Mancini). In almost 90% of cases of progressive, bilateral sensorineural hearing loss, serum antibodies were identified against a 68kD protein, today known as 'heat shock protein 70'(Rauch), while only 30% of patients with Meniere's syndrome, proved positive to a 30-32 kD protein (Filipo). Medical treatment of these forms, hypothetically dependent on the precise identification of the proteins in question (Carey), is still today based on the repeated dosage of steroids, or, in the case of refractory patients or those who become so, of immuno-suppressive treatment (Rauch, Salonna). In the future, he use of animal models could offer further and more practical information (Megerian), as could systematic study with electronic or optical microscopes of selected cases (McKenna).

Maurizio Barbara

For informations and/or communications to AUDIOLOGY-NEWSLETTER:
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Fax: +39-80-5478330

MDIC Special Report: The Round Window Micro-Catheter

Update, August 19, 2001 -- Durect (IntraEar) announces next generation ear catheter.

Update, March 12, 2001 -- Intraear has been acquired by Durect.

Update, May 26, 1999 -- IntraEar opens its doctor database to the Internet. According to IntraEar spokesperson Mike Arenberg, The doctors in this database have attended one of IntraEar's Strategic Think Tank Sessions or have attended a surgery where one of the IntraEar micro-catheters was inserted.

Update, Oct. 9, 1998 -- IntraEar has opened a beta website at www.intraear.com. This great website is the home page of the manufacturer of the Round Window Micro-Catheter and the Round Window E-Catheter.

Update, Sept. 13, 1998 -- IntraEar, Inc. (formerly Biometrix, Inc.), has released a second microcatheter device, called the round window triple-lumen micro-catheter, or e-cath. According to IntraEar spokesperson Mike Arenberg, the e-cath is IntraEar's second product, cleared by the FDA in March, 1998. It is the same as the round window micro-catheter [or m-cath or u-cath] except for a third lumen [channel] which contains and insulates an electrode for electrocochleography. The electrode is exposed on the distal tip of the catheter so that it contacts the internal wall of the round window niche. Placing the electrode tip in such close proximity to the round window membrane provides very robust ECoG recordings compared to standard transtympanic or ear canal electrodes, says Arenberg.

Update, Feb. 27, 1998 -- Dr. Michael Hoffer and his colleagues in the U.S. Navy now have treated a total of nine patients using the protocol described below (syringe and round window micro-catheter). Dr. Hoffer reports that the preliminary data (with stress on "preliminary") is that all nine patients are free of vertigo with improved tinnitus and pressure. Hearing loss in the patients is basically unchanged in most patients, based upon what is known so far. Plans are in the works for treating a patient using a small pump (rather than a syringe) to deliver the drug gentamicin to the round window in the middle ear via the micro-catheter [m-cath].

(1997) There aren't too many new developments in the treatment of Meniere's Disease (Morbus Meniere). One of the latest was reported by the U.S. Navy, which has implanted a new device called the round window micro-catheter into patients with Meneire's Disease, to further the treatment of the disease. Here are the details:

- **The Navy's press release:**

  Subject: Navy News Service -- 8 Oct 1997
  From: "Naval Media Center Publishing" <pubs@mediacen.navy.mil>
  Date: 1997/10/10 NNS4212.

San Diego doctors perform groundbreaking procedure by JO1 Joe Parker, Naval Medical Center San Diego Public Affairs

SAN DIEGO (NWSA) – A team of Naval Medical Center San Diego doctors performed a groundbreaking procedure in the treatment of Meniere's disease. Meniere's disease is a serious inner ear disorder that causes decreased hearing, dizziness, ear ringing and ear pressure. The team, which included physicians LCDR Michael Hoffer, Lt. Col. Richard Kopke, LCDR Loring Perry and staff vestibular specialist Dr. Derin Wester, became the first to implant a device known as the round-window micro-catheter into the ear of a patient with Meniere's disease.

"Until the development of the new procedure," said Hoffer, "the treatment for Meniere's disease consisted of a neurosurgical procedure or the injection of a large dose of Gentamicin, a toxic antibiotic, through the eardrum." The Medical Center team of doctors also performed all of the basic research studies establishing the safety of sustained release devices in the ear. "Three people out of one thousand are affected by Meniere's disease," said Hoffer, "which thanks to the Navy, now has a new, safer form of treatment."

The U.S. Navy Vestibular Balance Center provides patient care, education and research, and as a major DOD referral center for balance and hearing problems. The center also has a tremendous amount of ongoing clinical and basic research aimed at treating deafness and balance disorders.

- **Report (1997) on the round window micro-catheter, based upon an interview with the manufacturer and upon the manufacturer's literature.**

The round window micro-catheter is the first new device by IntraEar, Inc., a company founded by Dr. I. Kaufman Arenberg (inventor of the "Arenberg shunt") and his sons Michael and Daniel. According to the company, the new device "allows, for the first time, an accurate and controllable method of targeting the round window, at a minimal cost." Judging from text and **illustration** in company literature, the device is inserted through the tympanic membrane (ear drum) into a snug position in the bony niche in which the round window resides in middle ear, with the tip "approximately 1 mm from and facing the round window membrane." The tips come in three diameters: 1.5 mm, 2.0 mm, and 2.5 mm. "The round window membrane is the 'target' of both" the device and transtympanic needle injection. Tubing leads from the device through a grommet in the tympanic membrane to a pump located outside of the ear. Alternatively, a syringe may be connected to the tubing.

The company literature says that "[t]he inflow-outflow design is intended to allow the treating physician to, without removing the device, (1) add fluid, (2) remove fluid, (3) flush the device, and (4) relieve or avoid build up of air or fluid pressure."

A statement in company literature says that "[p]rior to using any fluid with the [device], the treating physician should check the fluid labeling to ensure that the fluid is labeled for that use." A company spokesperson told us that, under the terms of its government approval, the company could make no representations as to what fluid might be delivered. However, we will speculate, based upon other known treatments, that the fluids might include Gentamicin, Streptomycin, and/or Dexamethasone (remember, that's only our speculation).

Our conclusion is that rather than being a new treatment, the device provides a new method of delivering drugs to the round window, as an alternative to using a hypodermic needle passed through an opening in the tympanic membrane.

IntraEar, Inc., is located at 7995 E. Prentice Ave., Suite 110, Greenwood Village, CO 80111, USA; telephone (303) 850-0670; fax (303) 850-0671; email **company@intraear.com**.

[Note: This article was slightly revised on November 23, 1997, to include the fact that a syringe may be used instead of an exterior pump, and to better explain the positioning of the device into the bony niche in which the round window resides in the middle ear. It was revised on November 28, 1997, to

add the facts that there is a grommet placed in the tympanic membrane (ear drum) and that tips come in three sizes. It was revised on December 23, 1997, to add scanned images of the micro-catheter.]

- **Report (1997) based on an interview with Dr. Michael Hoffer, who has implanted and used the round window micro-catheter.**

  Doctors Lieutenant Commander Michael Hoffer, U.S. Navy, and Lieutenant Colonel Richard Kopke, U.S. Army, have implanted a new device called the "round window micro-catheter" manufactured by IntraEar, Inc., into four patients in treating their Meniere's Disease using the drug Gentamicin. According to Dr. Hoffer, the device permits a more accurate and controlled delivery of the drug than heretofore possible to the round window (a membrane in the middle ear), where the drug perfuses (passes through the round window) to the inner ear. The objective is for Gentamicin to destroy the so-called "dark cells" of the inner ear to control the vertigo caused by Meniere's Disease without impairing the patients' hearing function.

  Dr. Hoffer says that traditional treatment of Meniere's Disease without the round window micro-catheter varies, with a total of anywhere from 30 mg to 500 mg of the drug administered over anywhere from once a month to a couple of times in a single day, and the quantity actually delivered through the round window is not known. Drs. Hoffer and Kopke have implanted the round window micro-catheter into four patients with Meniere's Disease within the past six months. Based on studies on chinchillas, the doctors believe that a lower than traditional dose of Gentamicin, using the round window micro-catheter, can bring about improved results. In the four patients implanted so the doctors administered 2.5 mg of Gentamicin at the time of surgical implantation of the device (which Dr. Hoffer describes as "minor surgery"), followed by another 2.5 mg administered using the device a week after surgery. The device remained in place for two weeks following implantation. Patients did not have to lie in any particular position following the administrations of Gentamicin, and were free to walk around, etc., while the device was implanted.

  Dr. Hoffer says, "The 2.5 mg [of Gentamicin] is placed using a syringe to completely fill the catheter tip and catheter lumen. We know from our animal work that the medicine is delivered in a time release fashion as the Gentamicin in the solution at the tip is absorbed across the round window membrane the Gentamicin in the solution behind it moves to the tip and is available for absorption next. We know the kinetics of this delivery in animals (but not in humans). Obviously, a pump would provide a more sustained release. We are working with a pump that delivers a set amount per hour in our animal model and hope to begin human use in the next few months."

  Using traditional administration of Gentamicin, which involves making a hole in the eardrum with a laser beam and injecting the drug into the inner ear through the hole with a hypodermic needle, Dr. Hoffer says that improved results would not show up for days or weeks later. However, the improvement for the four patients who received Gentamicin through the round window micro-catheter was evident within 24 hours after the surgical implantation and first administration of Gentamicin. The results in the four patients implanted to date by the two doctors are the elimination of vertigo, plus (rarely seen with traditional administration of Gentamicin) a reduction in the tinnitus and feeling of pressure that are experienced by Meniere's Disease sufferers, all without the degradation of hearing that can occur with traditional administration of Gentamicin.

  Dr. Hoffer says that a controlled study using Gentamicin delivered by the new device is in developmental stages with various institutions, and that any institution that would like to participate is welcome to contact him or Dr. Kopke at the U.S. Naval Medical Center in San Diego. The administration of other drugs used to treat Meniere's Disease by perfusion through the round window, including steroids such as dexamethasone, lies in the not-too-distant future, says Dr. Hoffer.

  Dr. Hoffer's email address is **mhoffer@snd10.med.navy.mil**; his telephone number is 1-619-532-6964.
  IntraEar, Inc., is located at 7995 E. Prentice Ave., Suite 110, Greenwood Village, CO 80111, USA; telephone (303) 850-0670; fax (303) 850-0671; email **c mpany@intraear.com**.

Research into the Treatment and Prevention of Noise-Induced Hearing Loss

By CDR Glen Rovig, MSC
Operational Audiology Officer

YOU HAVE PROBABLY SEEN some recent national publicity concerning research into new types of treatment and prophylaxis for sensorineural hearing loss. Two researchers at NAVMEDCEN San Diego are working with a micro-catheter to deliver medication to the cochlear fluids via absorption through the round window. They (and others) are also looking at the contribution of free radicals to noise and toxin-induced hearing loss, and the preventive effects of antioxidants. After doing some background reading, I communicated with one of the researchers, otolaryngologist LCDR Mike Hoffer, MC, USN. He was kind enough to answer a series of questions for me, and I thought the information might be useful to the Occupational Health community.

First, a few basics:

Loud noise causes reduced microcirculation within cochlear blood vessels.

This somehow releases higher than normal numbers of radical oxygen species (ROS) or "free radicals" which can react with and damage cellular protein, DNA, and unsaturated lipids. (My grasp of autocatalytic events is a bit tenuous, so I cannot give you much clarification here.)

The body's normal antioxidant defenses cannot counter the excess free radicals. TTS and PTS may follow with prolonged noise exposure. This is a gradual, noise-induced permanent threshold shift model, as opposed to acoustic trauma, which may physically damage the tectorial and/or basilar membranes and associated structures.

One study involving chinchillas is representative. Each animal was

treated with saline (control) applied to the distal surface of one round window membrane, and an antioxidant applied to the opposite round window. The animals were then exposed to 4 kHz noise at 105 dBSPL for four hours. Antioxidant-treated ears showed significantly less TTS and reduced PTS as well as significantly less outer hair cell loss compared to the control ears.

Augmenting the antioxidant defense system with additional "free radical scavengers" holds promise for preventing/minimizing hearing loss from toxins and noise exposure.

A second area of research is delivering medications to the cochlear fluids via micro-catheter. Entering the middle ear via a small hole in the TM, the catheter is placed against the round window, where medication is absorbed through the membrane over a period of several days. A major benefit is that medication goes directly to the target area and avoids side effects associated with oral administration.

Here are LCDR Hoffer's replies to my emailed questions:

Q: What types of patient care are being envisioned for the catheter?
A: The catheter is a FDA-approved device for irrigation of the round window membrane. We have done all of the pioneering basic research with the device and had the original and largest experiment on humans. The catheter is, however, being used for multiple indications at other (select) institutions. Most of these institutions are following protocols which we established. Indications for the catheter include, but are not limited to, Meniere's Disease, sudden sensorineural hearing loss of a variety of etiologies, tinnitus treatment, and toxic insults to the inner ear (hearing and balance). The catheter has been used on approximately thirty patients at our institution. Six patients with sudden hearing loss have been treated. All three patients who were seen in under four weeks showed a dramatic improvement after treatment. The other three patients seen (longer time since injury) had no improvement. Contraindications to catheter use include all standard ear surgery contraindications and all contraindications to surgery. We have seen no complications directly caused by the catheter.

Q: Is there any projection to use catheters to deliver anti xidants to humans, either before or after noise exp sure?
A: The treatment of inner ear disorders (hearing and balance) is a complicated issue. For many disorders the treatment depends on

using the right medicine (antioxidant, etc.) and having the appropriate concentration reach the target organ at the appropriate time. If oral administration achieves this end, and surgery can be avoided, that's fine. Undoubtedly, certain medicines (and certain antioxidants) will need to be delivered in an other than oral fashion. Severe sudden noise induced hearing loss (e.g. after a blast injury), is one example, of a disorder that may only be rescued with microcatheter delivery of antioxidants. Prophylaxis will be accomplished through some type of oral medication.

Q: The news release focuses on prednisone/steroid therapy for acute cochlear conditions. Is there an application for prednisone with NIHL? Does prednisone act the same way as an antioxidant?
A: There is basic science work that indicates that corticosteroids can rescue noise induced hearing loss and have antioxidant properties. Methylprednisolone, for example, up-regulates antioxidant enzyme activity in neural tissue. It also has other effects such as neuroprotection, increasing cochlear blood flow, and antiapoptotic and anti-inflammatory effects.

Q: Any projection for how soon someone will start delivering antioxidants orally as prophylaxis for NIHL? Sounds like there are some FDA-approved substances used for other applications (per Kopke, Feghali and Henderson). When/where will there be trials?
A: We have already used an FDA-approved oral agent for rescue of noise induced hearing loss. Basic science studies are being completed in the area of prophylaxis and pre-clinical trials are now underway. We, and others, anticipate clinical trials in under two years.

Q: The news release quotes $1.5 billion annually going toward treatment of NIHL. Where does that figure come from?
A: The $1.5 billion dollar figure was for both hearing and balance disorders. The figure breaks down to $1 billion on hearing and $500 million on balance. Many individuals feel this is an underestimation of costs. The costs include lost equipment, cost of lost training in combat arms, VA compensation, and expenditures for civilian hearing loss compensation charged back to installation commanders. This figure came from NAMRL and from the Chairman of the DoD Working Group on Hearing Conservation.

Q: D you have any projected cost data for the catheter? H w is your catheter different fr m the others in use for applying medications to the middle ear?
A: There is currently no other catheter available and the current catheter is patent protected by IntraEar Corporation. The cost of the catheter is approximately $650 depending on the number bought.

Q: Is it fair to say that we are in the basic science stage with respect to understanding the damaging effects of ROS and the protection afforded by antioxidants? In your opinion, are oral doses of antixodants likely to be a part of our Hearing Conservation Program anytime soon?
A: There is still basic science to be done in this area, but enough is understood about this problem that currently a large clinical study is underway to evaluate the effectiveness of an antioxidant to prevent hearing loss secondary to ROS generation after aminoglycoside administration (similar mechanism to NIHL). We have already used an oral antioxidant as rescue mode and oral antioxidants are very likely to be part or our hearing conservation program in the next three years.

Q: We have seen 2 articles with Dr. Kopke as co-author and they appear to be drafts. Have you published anything?
A: Between Dr. Kopke and me we have over seventeen published articles and dozens of abstracts on hearing and balance disorders relating to protection, rescue, and restoration of function of the inner ear. Dr. Kopke has ten published articles in peer-reviewed journals in the area of protection/rescue of the inner ear from toxins/noise. Several others are in press. Together we have two published articles on inner ear delivery of medicines and have several in press. In addition, we have over ten abstracts addressing inner ear medicine delivery in the last three years. We are presenting four abstracts of our latest work at the 1999 Association for Research in Otolaryngology Midwinter Meeting (February 1999). We also have several additional papers and chapters submitted or in press.

Q: LCDR Keith Wolgemuth (NMCSD Audiologist) tells us you are also doing animal work at NMCSD. What is the focus of that work? Can you summarize?
A: The big picture is that we are researching medicines, and delivery methods for those medicines, to protect and restore inner ear hearing and balance function. The focus of the animal work is delivery of medicines to the inner ear, the effects of medicine on the inner ear, prevention and rescue of NIHL with medicines, and

prevention and rescue of inner ear damage from high-energy, low frequency sound underwater. A majority of these projects are highly operational and at pre-clinical stages. One of the projects involves vital national security issues.

Q: What we have read in the press about your work has been extremely optimistic, e.g., a cure for hearing loss is right around the corner. Are you comfortable with what is being said?

A: We don't feel that the articles (and there have been many of them) actually say, "a cure for hearing loss is right around the corner." Of course, we are not always comfortable with what the press says - but we can't completely control the press and all briefings have been conducted while a Navy PAO was present. We made a point that while the research is exciting; it is still somewhat preliminary and needs additional funded study. There is reason for optimism regarding prevention and reversal of many types of hearing and balance disorders, because ROS are involved with many different etiologies of inner ear damage including noise induced hearing loss, toxic injury, autoimmune disease, viral disease, and aging as well as some genetic predisposition to hearing loss. Since there is a final common pathway for injury and we understand the mechanism, therapy can be designed based on this understanding.

Q: Any other comments?

A: ...we and other capable in-house (within DoD) workers are advancing the field of hearing and balance science. For example, capable, in-house individuals exist at our center, at NAMRL, and at NSMRL. Only by doing the work in-house will the therapies be made available to active duty individuals at the earliest possible times. For years the National Institute of Health requested grants for transitional research of NIHL and discovered that no single group (other than ours) had the appropriate population. Therefore, much of the NIH grant money has gone to basic work, which is far from impacting active duty individuals. The Office of Naval Research has already said that in the area of balance the end-user (to implement new developments in motion sickness) will be the DSOC in San Diego and have acknowledged that we are the only facility with the appropriate target population for large scale implementation of projects with regards to hearing loss prevention and rescue.

Dr. Kopke has been working in this area since 1994 and initially worked to prevent and reverse hearing loss due to toxins by

counteracting ROS effects. He saw that the concept of ROS damage might be pertinent to NIHL, introduced those concepts and designed initial experiments in Dr. Henderson's lab beginning in 1995. Those initial experiments were successful and have spawned additional work, including the work here at NMCSD. Dr. Henderson utilized Dr. Kopke's expertise as a consultant to successfully compete for a program project grant. Dr. Kopke has been invited by the NIDCD and the ARO to share his expertise in this field at targeted symposiums.

A number of other experienced investigators (i.e. Dr. Jochen Schacht, Dr. Joe Miller, and researchers at the Karolinska Institute) agree that clinical trials to prevent NIHL are likely within the next two years, and have asked for Dr. Kopke's help to accomplish this. The Peoples Republic of China is actively pursuing this line of research and such work has the potential to give their forces a tactical advantage.

I have led our group in work with delivery of medicine to the inner ear for the last five years and we are recognized experts in this area. Dr. Kopke's expertise with therapeutic agents combined with our group's expertise on drug delivery to the inner ear provides a unique research team capability ideally suited to taking this research to the deck plates. The combined efforts of Dr. Kopke, the individuals in place at NMCSD, and me allows us to take work from the bench top to the active duty population delivering the therapeutic modality (medicine) in a number of possible fashions.

LCDR Hoffer and LTC Kopke, his co-researcher, have a couple papers in press and four presentations upcoming at the Assocation for Research in Otolaryngology meeting. One helpful article may be found in Otolaryngology-Head and Neck Surgery, Dec 93, "The Protective Effects of Allopurinol and Superoxide Dismutase on Noise-induced Hearing Loss" (Seidman et al).

MAA Contents | Newsletter Contents | Airbag Deployment | Committee for Audiology Research | President's Message | Operation BANG | Specialty Recognition | Audiology Awareness | Army News | Navy News

ALZET®

IntraEAR®

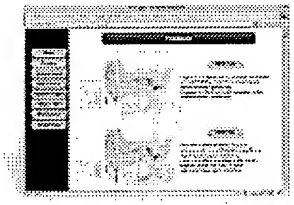
Birmingham Polymers

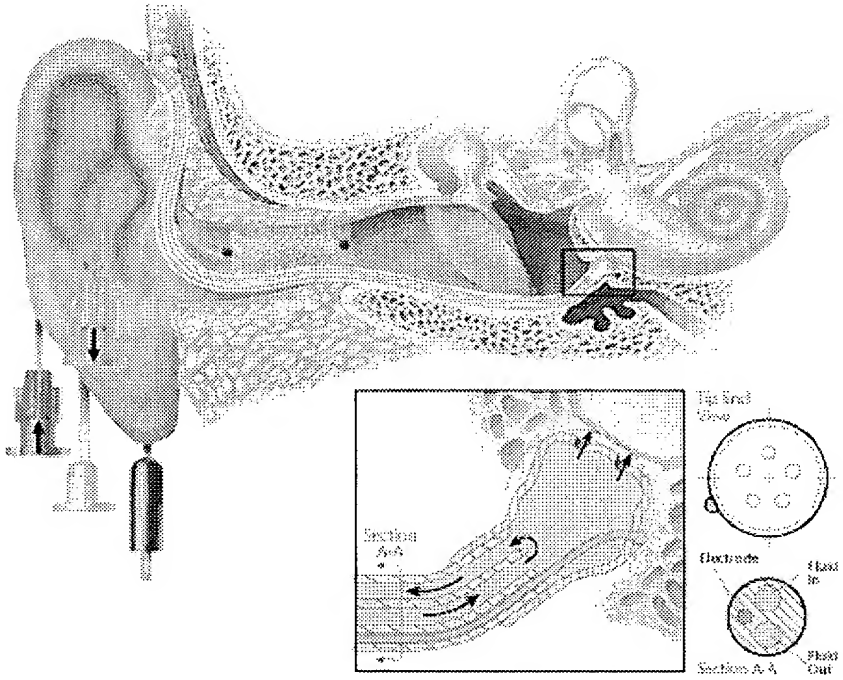
Partnerships

IntraEAR®

DURECT currently sells the IntraEAR® Round Window μ-Catheter™ (RWμ-Cath™) and Round Window E-Catheter™ (RWE-Cath™) products, both of which have received 510K marketing clearance from the FDA and European CE Mark approval. We acquired these products as part of our acquisition in October 1999 of IntraEAR, Inc.

For more information about the IntraEAR® Round Window μ-Cath™ and Round Window E-Cath™ visit www.intraear.com





The RWμ-Cath™ and RWE-Cath™ products are dual- and triple-lumen micro-catheters of proprietary design, which allow controlled fluid delivery to the round window membrane of the middle ear. Physicians have used these catheters to treat a variety of ear c
proprietary tip, which is designed t
round window niche of the middle
up to 29 days and can be connect
manufactured by Disetronic Medic
fluids to the round window membr
treating physician to add and remc
build up of fluid or air pressure. Th
electrode to allow physicians to re
function before, during or after tre

Applicant

For more information about the IntraEAR® Round Window μ-Cath™ and Round Window E-Cath™ visit www.intraear.com.

Back to top

Last updated: May 20, 2002

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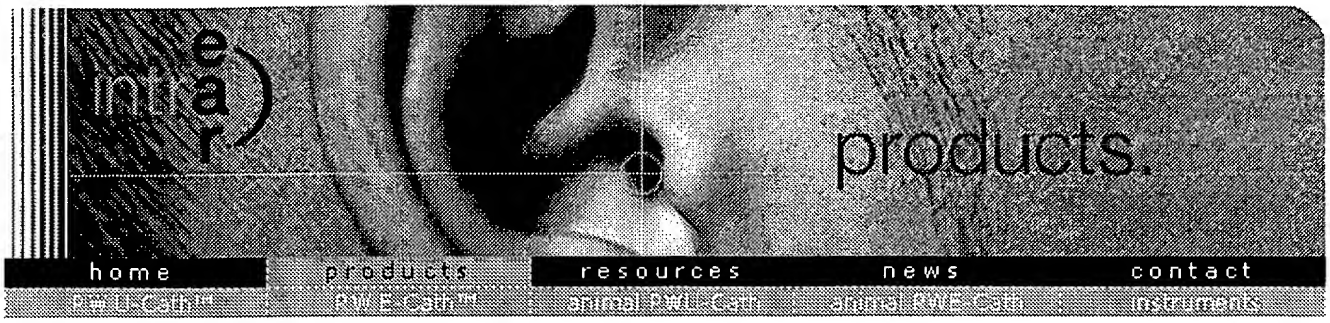
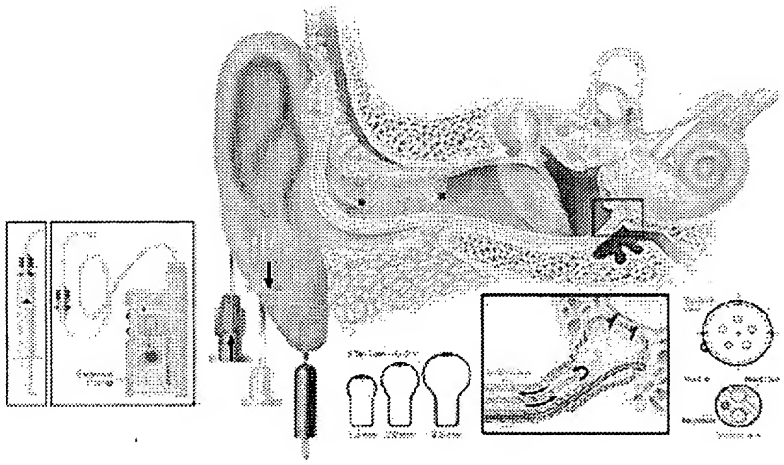


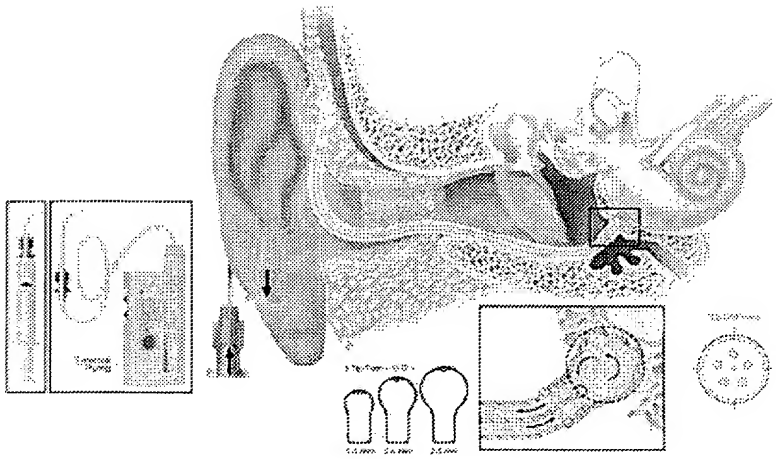
Traditionally, administering medication to specific sites in the ear for the treatment of ear disorders has been difficult and imprecise.

With DURECT's innovative IntraEAR® line of catheters, physicians can now administer fluids directly to the round window membrane in a precise and controlled manner. Although the IntraEAR® catheters are not indicated for the delivery of specific fluids for the treatment of specific ear disorders, physicians currently use the IntraEAR catheters to treat a number of ear disorders such as Meniere's disease, Sudden Sensorineural Hearing Loss and Tinnitus.



Round Window E-Cath™ (RWE-Cath™)

DURECT's IntraEAR Round Window E-Cath (RWE-Cath) is a triple-lumen micro-catheter specifically designed to allow controlled targeting of the round window membrane and accurate electrocochleography recording.



Round Window μ Cath™ (RWμCath™)

DURECT's IntraEAR Round Window μ Cath (RWμCath) is a dual-lumen micro-catheter specifically designed to allow controlled targeting of the round window membrane.

Instruments

DURECT's IntraEAR® line of stainless-steel instruments facilitates proper placement of the IntraEAR® line of catheters in the round window niche.

Avhandlingar från Uppsala universitet

Avhandlingen är publicerad vid **Institutionen f¨r kirurgiska vetenskaper, Enheten för öron-, näs- och halssjukdomar**

Nordang, Leif: The Round Window Membrane - Gateway to the Cochlea : A Morphological and Electrophysiological study. - Uppsala, 2002. - 33p. - (Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine, ISSN 0282-7476 ; 1134)
ISBN 91-554-5277-9
Abstract: HTML | PDF (kräver Acrobat 5) | Se bibliotekskatalogen
Fulltext: Köp boken online

ABSTRACT

Topical treatment of several inner ear diseases through the round window membrane (RWM) might be feasible in the near future. Bacteria toxins, ototoxic drugs and noise trauma seem to harm the inner ear by a common pathway which involves, excessive outflow of the afferent neurotransmitter glutamate and formation of nitric oxide (NO), which can severely damage cells/nerve endings and lead to cell death.

In this study we used 98 Sprague-Dawley rats and seven human temporal bones. Various substances were instilled into the middle ear of the rat, such as Pseudomonas Aeruginosa Exotoxin (PaExoA), gentamicin, NO-inhibitor N-Omega-Nitro-L-Arginine Methyl Ester (L-NAME), and glucocorticoids. The effects of the substances were studied by morphological analysis of RWM and the endolymphatic sac (ES) by light and electron microscopic. Hearing level was measured in the rats by ABR technique. The human temporal bones were studied immunomorphologically to search for glutamate.

In the human inner ear, glutamate receptors and glutamine synthetase, were identified. In the rat, we found, following PaExoA exposure, reversible and permanent hearing loss and morphological changes in the RWM. The ES showed increased numbers of macrophages and thickening of the epithelia. When L-NAME was used as an otoprotector from gentamicin ototoxicity a therapeutic effect in the high frequency area was found. Hydrocortisone (but not dexamethasone) exposure of the RWM resulted in membrane thickening, and adjacent to the membrane, inflammatory cells.

The importance of the RWM as a portal for toxic substances and topical treatment of inner ear diseases was highlighted in this study. The difficulties of applying drugs in the round window niche were exposed. The results of this study add important knowledge concerning certain mechanisms of inner ear injury and help us to understand possibilities and problems of local treatment of inner ear diseases in patients.

List of papers:

I. Nordang L., Anniko M.. (2001). Hearing loss in relation to round window membrane morphology in experimental chronic otitis media. *ORL* 63: 333-340

II. Nordang L., Anniko M., Rask-Andersen H.. (2001). Middle ear exotoxin and endolymphatic sac response: an immune reaction?. *Oto-Rhino-Laryngologia Nova* 10: 269-276

III. Nordang L., Oestreicher E., Arnold W., Anniko M.. (2000). Glutamate is the afferent neurotransmitter in the human cochlea. *Acta Otolaryngol* 120: 359-362

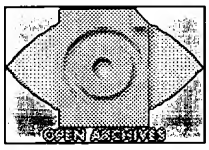
IV. Nordang L., Anniko M.. L-NAME, a potential protector from gentamicin ototoxicity. (Submitted)

V. Nordang L., Linder B., Anniko M.. Morphological changes in round window membrane following topical hydrocortisone and dexamethasone treatment. (Submitted)

Keywords: round window membrane, pseudomonas exotoxin, auditory brainstem response, hearing loss, endolymphatic sac, inner ear immunology, glutamate, nitric oxide inhibitor, glucocorticoid.

Disputation: 2002-05-03 kl. 13:15, Skoogsalen, ingång 78/79, 1
Ämne: oto-rhino-laryngologi
Fakultetsopponent: Professor Sten Hellström, Umeå, Sverige

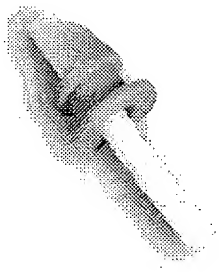
Ladda ner referens: Dublin Core | MARC 21 | RIS (Reference Manager, Endnote etc.)



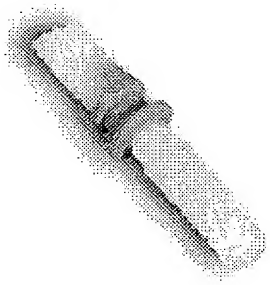
Otology Products

▶ Silverstein MicroWick™

The MicroWick aids in the treatment of Menieres Disease and other types of Inner Ear Disease.



MicroWick, dry



MicroWick, hydrated

- Permits direct treatment of the diseased ear
- Aids in the treatment of Menieres Disease
- Simple, inexpensive office procedure
- Helps treat Menieres Disease with less complications
- Allows for continuing patient self-treatment
- Excellent clinical results[1]

Procedure

In this procedure, which can be performed in the office, the MicroWick sponge is placed through a special tympanic membrane vent tube onto the round window membrane. The correct location of the myringotomy can be established by visualizing the round window membrane through the tympanic membrane, or by approximating the location of the round window membrane using anatomical landmarks.

The dry compressed wick inserts easily before hydration. After insertion, the wick is hydrated by placing fluid medication into the external ear canal. Fluid applied to the MicroWick is transported directly to the round window membrane. The hydrated wick expands to lock securely in place.

Patients can continue daily self-treatments by placing drops into the ear canal. Treatments usually last from two to four weeks. After treatments are concluded, the wick and tube are removed together as a single unit. The wick and tube can be removed in the office without anesthesia.

[1] Silverstein, Herbert, MD, FACS; "Use of a new device, The MicroWick, to deliver medication to the inner ear"; ENT – Ear, Nose and Throat Journal, August 1999.

To read more about the Silverstein MicroWick, visit the Florida Ear and Sinus Center website.

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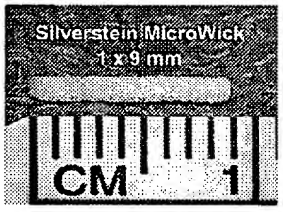
FLORIDA EAR & SINUS CENTER

RealVideo clip of the MicroWick™ procedure described below.
To view this video, you'll need to download the free RealPlayer G2.

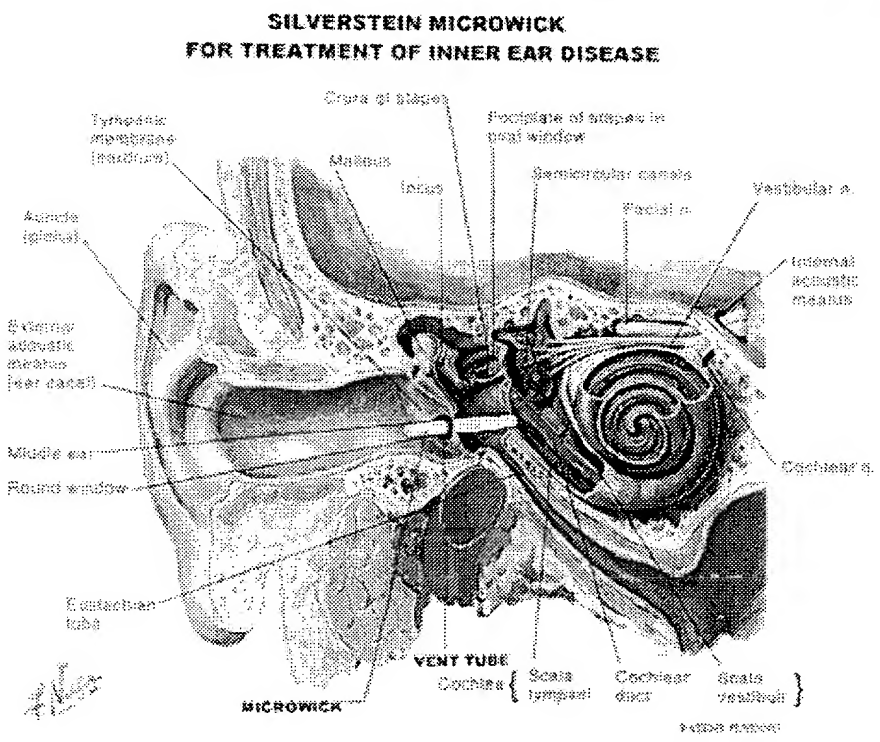
A new technique for self-treating Ménière's & Inner-ear Disease using the

SILVERSTEIN MicroWick

More Information:
Allergies
Ear Infections
LaserSTAMP
Meniere's Disease
Minimally invasive surgery
OtoLAM
Otosclerosis
Pediatric ENT
Sinus Surgery
Skull base tumors
Snoring
Taste & smell



The antibiotic gentamicin when placed in the middle ear is an effective method of relieving attacks of Ménière's disease in 80% while preserving the hearing in 95%. These results have been obtained using a MicroWick™ and tube manufactured by Micromedics of Minnesota. The MicroWick™ is placed through a tiny tube in the eardrum and then rests on the round window membrane, the doorway to the inner ear.



THIS NEW TECHNIQUE developed by Dr. Herbert Silverstein uses dilute gentamicin otic solution (5-10 mg/cc) that the patient places in their ear three times a day for two to three weeks. This method is similar to treating eye diseases with eye drops. Thus far the results have excellent in relieving vertigo attacks and preserving the patients' hearing. Also, in 60% of patients the pressure and tinnitus have been reduced.

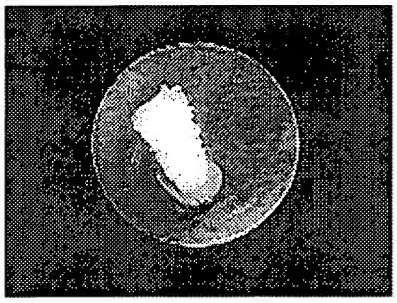
The minimally invasive office procedure is done using local anesthesia. The ESC Sharplan CO2 laser is used to create a bloodless opening in the

disorders

Tinnitus

Vestibular rehabilitation

eardrum through which a tiny endoscope is inserted. Any obstructing membranes near the round window membrane are easily removed with an instrument before the MicroWick™ is inserted. Next, a tiny tube is inserted in the tympanostomy opening. Now the round window membrane is clearly seen and the Silverstein Inner Ear MicroWick™ is inserted. This allows the gentamicin to reach the round window membrane and diffuse into the inner ear fluids, which will eliminate the dizziness of Ménière's disease in 80%.



The treatment is inexpensive, easy, painless, and well tolerated by the patients. After the treatment, the tube and the MicroWick™ are easily removed in the office. The opening in the eardrum rapidly heals. There have been few complications and the results have been excellent.

The MicroWick™ technique represents an exciting new method for treating Ménière's disease and allows the delivery of medications, as they are developed, to treat various inner ear diseases such as ringing in the ears (tinnitus) and certain types of deafness.

Click here for research paper summaries:

1) Self-treatment of inner ear disease using otic medication delivered by the Silverstein MicroWick™

2) Use of a new device, the MicroWick™ to deliver medication to the inner ear

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Ear Research Publication Summaries

The following are summaries from the latest publications from the Ear Research Foundation. Click on the title below to go directly to the summary.

Dexamethasone inner ear perfusion for the treatment of Meniere's disease - A prospective, randomized, double-blind, crossover trial.

Objective: To investigate the benefits of intratympanic administration of dexamethasone in the treatment of unilateral Ménière's disease, with particular attention to the symptoms of hearing loss and tinnitus.

Study Design: A prospective, randomized, double-blind, crossover study comparing improvements in hearing loss, tinnitus, aural fullness, and caloric vestibular response secondary to intratympanic dexamethasone and sodium hyaluronate injection versus placebo consisting of saline and sodium hyaluronate.

Setting: A private otology/neurotology practice.

Patients: Twenty patients diagnosed with either definite or probable Ménière's disease as defined by the American Academy of Otolaryngology head and Neck Surgery committee on hearing and Equilibrium. All patients were ? 21 years old and were not receiving any other form of treatment for their Ménière's disease. Each patient's primary symptoms of concern were hearing loss, aural fullness, and roaring tinnitus.

Interventions: Three consecutive daily administrations of intratympanic dexamethasone or placebo to the involved ear.

Main Outcome measures: Changes in audiometric pure-tone averages,

Direct round window membrane application f gentamicin in the treatment of Meniere's disease

The direct RWM gelfoam application of gentamicin was used to treat 32 patients with Meniere's disease. This is a minimally invasive procedure that can be performed in the office. An otoendoscope is passed through a laser assisted tympanostomy and the RWM is directly visualized. Gelfoam is applied to the RWM, clearing the RWM if necessary. The middle ear is then injected with gentamicin. Three protocols were evaluated. Although long term follow-up is necessary, we believe this method will help eliminate some of the inconsistent results using blind transtympanic injections of gentamicin. Protocol #2 emerged as the best clinical protocol and showed a 71% control of vertigo improvement in aural pressure in 62% and improvement in tinnitus in 60% of patients. In this, patients received two gentamicin infusions five days apart. This approach is also a useful alternative for surgical salvage in cases of recurring vertigo following an ablative procedure for Meniere's disease and can be helpful in the conservative management of small acoustic neuromas when the patient has coincident Meniere's disease in the same ear. The direct RWM gelfoam gentamicin technique is an efficient, cost-effective procedure which can effectively control vertigo in 75% of cases while improving aural pressure (62%) and tinnitus (48%).

Use of a new device, the MicroWick, to deliver medication to the inner ear

A new procedure for delivering medication directly to the inner ear has been developed. This delivery system, called the MicroWick, involves the use of a small wick that is inserted through a tympanic membrane vent tube into the round window niche. Once the wick has been inserted, the patient can self administer eardrops into the ear canal, where they are absorbed by the wick and transported to the round window membrane and to the inner ear fluids. Inserting the wick is a minor procedure that is performed in the office. This paper describes the indications for and use of the MicroWick.

More information is available on the MicroWick home page.

Self-treatment of inner ear disease using otic medication delivered by the Silverstein MicroWick

Perfusion of the inner ear using various medications is becoming a more popular form of treatment of inner ear disease. The advantages of placing medications directly into the inner include: 1. The diseased ear is treated directly without affecting the entire body. 2. A higher concentration of medication can be obtained. 3. Systemic side-effects of the drug are prevented.

Techniques thus far involve direct injection of medication through the tympanic membrane into the middle ear; direct injection of medication though a tympanostomy opening onto Gelfoam that has been placed in the round window niche; direct injection though a micro catheter that has been inserted into the round window niche. The, latter method, insertion of the micro catheter is performed in the hospital and can be quite expensive.

A safer, simpler, and more cost-effective procedure for treatment of inner ear disease is needed. A method has been developed similar to the current self-treatment for eye disease using medicated eye drops. Because the inner ear lies inaccessible behind the tympanic membrane, this method of self-treatment has eluded us in the past. The new method utilizes a MicroWick that is inserted through a tympanic membrane vent tube onto the round window membrane. The patient places the medication into the ear canal which is absorbed by the MicroWick and transported to the round window membrane to the inner ear fluids.

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1/9/1 **(Item 1 from file: 350)**
DIALOG(R)File 350:Derwent WPIX

013474587 **Image available**
WPI Acc No: 2000-646530/200062
XRAM Acc No: C00-195465
XRPX Acc No: N00-479121

Orthological implant and medicament delivery for treating inner ear disease, implant has wick which conveys medicament to treatment site by capillary action

Patent Assignee: SILVERSTEIN H (SILV-I)
Inventor: **SILVERSTEIN H**
Number of Countries: 001 Number of Patents: 001
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
US 6120484	A	20000919	US 99120327	A	19990217	200062	B
			US 99287344	A	19990407		

Priority Applications (No Type Date): US 99120327 P 19990217; US 99287344 A 19990407
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
US 6120484	A		8	A61M-031/00	Provisional application US 99120327

Abstract (Basic): US 6120484 A

NOVELTY - The implant (10) comprising a medicament-free wick (12) whose distal end (14) contacts the treatment site, and proximal end (16) contacts the medicament source. The wick body (18) is sized to fit in an aperture in a membrane and the medicament is conveyed to the treatment site by capillary action.

DETAILED DESCRIPTION - The implant (10) comprising a medicament-free wick (12) whose distal end (14) contacts the treatment site, and proximal end (16) contacts the medicament source. The wick body (18) is sized to fit in an aperture in a membrane and the medicament is conveyed to the treatment site by capillary action. The implant is also provided with a tube member (20) which acts as a grommet when inserted in the membrane aperture. After implantation the first end (22) of the tube is on one side of the membrane and the second end (24) is on the other side. The tube is prevented from dislodging by means of a flanges (28,30) around a concave body (26) which facilitates the seating of the tube in the membrane aperture.

USE - For treatment of inner ear disease by delivering medicament from one side of the membrane to the treatment site on the other side of the membrane.

ADVANTAGE - The cost and time efficiency are improved.

DESCRIPTION OF DRAWING(S) - The drawing shows a side view of the implant

Implant (10)
Wick (12)
Wick distal and proximal ends (14, 16)
Wick body (18)
Tube (20)
Tube ends (22, 24)
Tube concave body (26)
Flanges (28, 30)
pp; 8 DwgNo 1/10

Technology Focus:

TECHNOLOGY FOCUS - POLYMERS - Preferred Wick: The wick can be made of polyvinyl acetate. The tube member can be made of nylon.

METALLURGY - Preferred Tube: The tube member can be made of titanium, titanium alloy, stainless steel or silicon.

Title Terms: IMPLANT; MEDICAMENT; DELIVER; TREAT; INNER; EAR; DISEASE; IMPLANT; WICK; CONVEY; MEDICAMENT; TREAT; SITE; CAPILLARY; ACTION
Derwent Class: A96; B07; D22; P34
International Patent Class (Main): A61M-031/00
File Segment: CPI; EngPI

Manual Codes (CPI/A-N): A04-F08; A05-F01E3; A12-V01; B11-C04A; B14-N02; D09-C01
Chemical Fragment Codes (M1):
01 H7 H713 J0 J011 J2 J271 M210 M211 M212 M262 M272 M281 M423 M424 M430 M510 M520 M530 M540 M740 M782 M904 M905 N105 RA012N-K RA012N-M
Chemical Fragment Codes (M2):
03 A422 C810 M411 M424 M430 M740 M782 M904 M905 N105 R10714-K R10714-M
04 B114 C810 M411 M424 M430 M740 M782 M904 M905 M910 N105 R01666-K R01666-M
Chemical Fragment Codes (M6):
05 M905 Q110 R046 R430
Polymer Indexing (PS):
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Derwent Registry Numbers: 1666-U; 2035-U
Specific Compound Numbers: RA012N-K; RA012N-M
Key Word Indexing Terms:
01 104491-0-0-0-CL 102573-0-0-0-CL 1463-0-0-0-CL 107015-0-0-0-CL
?

09/205,251

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L1 ANSWER 1 OF 1 DPCI (C) 2002 THOMSON DERWENT
AN 2000-646530 [62] DPCI
DNN N2000-479121 DNC C2000-195465
TI Orthological implant and medicament delivery for treating inner ear disease, implant has wick which conveys medicament to treatment site by capillary action.
DC A96 B07 D22 P34
IN SILVERSTEIN, H
PA (SILV-I) SILVERSTEIN H
CYC 1
PI US 6120484 A 20000919 (200062)* 8p A61M031-00 <--
ADT US 6120484 A Provisional US 1999-120327P 19990217, US 1999-287344 19990407
PRAI US 1999-120327P 19990217; US 1999-287344 19990407
IC ICM A61M031-00
FS CPI GMPI

EXF EXAMINER'S FIELD OF SEARCH UPE: 20001211

NCL US 6120484 A 20000919
424/422; 424/427; 424/437; 604/164; 604/021; 604/264; 604/500; 604/501;
604/506; 623/011; 623/012; 623/066

CTCS CITATION COUNTERS

PNC.DI	0	Cited Patents Count (by inventor)
PNC.DX	23	Cited Patents Count (by examiner)
IAC.DI	0	Cited Issuing Authority Count (by inventor)
IAC.DX	1	Cited Issuing Authority Count (by examiner)
PNC.GI	0	Citing Patents Count (by inventor)
PNC.GX	0	Citing Patents Count (by examiner)
IAC.GI	0	Citing Issuing Authority Count (by inventor)
IAC.GX	0	Citing Issuing Authority Count (by examiner)
CRC.I	0	Cited Literature References Count (by inventor)
CRC.X	2	Cited Literature References Count (by examiner)

CDP CITED PATENTS UPD: 20001211

Cited by Examiner

CITING PATENT	CAT	CITED PATENT	ACCNO
US 6120484	A	US 2642065	A
	IN:	NEGRI; NEGRI, M	
		US 3807409	A 1974-36205V/19
	PA:	(MEDI-N) MEDICAL PRODUCTS CORP	
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	PA:	(GLAS-N) GLASROCK PROD INC	
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	PA:	(RICH-N) RICHARDS MEDICAL CO	
	IN:	KRYGIER, K; SANDER, T W	
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	PA:	(MINN) MINNESOTA MINING & MFG CO	
	IN:	MUCHOW, D C; SIRVIO, L M	
		US 5421818	A 1995-170006/22
	PA:	(INNE-N) INNER EAR MEDICAL DELIVERY SYSTEMS INC	
	IN:	ARENBERG, I K	

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PA: (INNE-N) INNER EAR MEDICAL DELIVERY SYSTEMS INC
IN: ARENBERG, I K
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PA: (INNE-N) INNER EAR MEDICAL DELIVERY SYSTEMS INC
IN: ARENBERG, I K
US 5503848 A 1993-046814/06
PA: (FIDI-N) FIDIA SPA
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PA: (ATRI-N) ATRIX LAB INC
IN: DUNN, R L; TIPTON, A J

REN LITERATURE CITATIONS UPR: 20001211

Citations by Examiner

CITING PATENT	CAT	CITED LITERATURE
US 6120484	A	L. Duberstein, "Intraluminal Tube Wick," Otolaryngology-Head and Neck Surgery, vol. 94, No. 1, Jan. 1986, pp. 135-136.
US 6120484	A	Commercial brochure from Americal Corporation for "Duberstein Intralumenal Tube Wick," publication date believed to be prior to 1999.

=>

?t s2/9/1

2/9/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05102562 86148032 PMID: 3081850
Intraluminal tube wick .
Duberstein L E
Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery (UNITED STATES) Jan 1986, 94 (1) p135-6, ISSN 0194-5998 Journal Code: 8508176
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Subfile: INDEX MEDICUS
Tags: Human
Descriptors: *Middle Ear Ventilation--instrumentation--IS; Middle Ear Ventilation--methods--MT
Record Date Created: 19860331

?show files
File 348:EUROPEAN PATENTS 1978-2002/May W02
(c) 2002 European Patent Office
File 349:PCT FULLTEXT 1983-2002/UB=20020516,UT=20020509
(c) 2002 WIPO/Univentio
?t s5/3,ae/5

5/3,AE/5 (Item 4 from file: 349)
DIALOG(R)File 349:PCT FULLTEXT

00474712
METHOD FOR PREVENTING AND TREATING HEARING LOSS USING A NEURTURIN PROTEIN PRODUCT
PROCEDES DE PREVENTION ET DE TRAITEMENT DES PERTES D'AUDITION A L'AIDE D'UN PRODUIT PROTEIQUE DE NEURTURINE
Patent Applicant/Assignee:
AMGEN INC,
Inventor(s):
MAGAL Ella,
DELANEY John M,
Patent and Priority Information (Country, Number, Date):
Patent: WO 9906064 A1 19990211
Application: WO 98US14600 19980717 (PCT/WO US9814600)
Priority Application: US 9754184 19970730; US 98106486 19980629
Designated States: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW GH GM KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG
Publication Language: English
Fulltext Word Count: 25776

English Abstract
The present invention relates generally to methods for preventing and/or treating injury or degeneration of cochlear hair cells and spiral ganglion neurons by administering a neurturin neurotrophic factor protein product. The invention relates more specifically to methods for treating sensorineural hearing loss.
?

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?ds
Set     Items   Description
S1        237   ROUND()WINDOW? OR RWM
S2      61659   (CONTROL? OR DELAY? OR SUSTAIN?)(3N)(DELIVER? OR RELEASE? -
             OR TARGET?)
S3     288969   DRUG? OR MEDICATION? OR MEDICINE? OR ANTIBIOTIC? OR DOSAGE?
              OR DOSE? OR DROPS? OR MEDICINAL? OR PHARMACEUTIC? OR REMEDY -
             OR REMEDIES OR MEDICINAL? OR MEDICANT?
S4         27   S1 (5N)2
S5          7   S4 AND S3
S6         29   S1 AND S2 AND S3
S7         12   S6 AND PY<1999
S8         10   S7 NOT S5
?show files
File 348:EUROPEAN PATENTS 1978-2002/May W02
         (c) 2002 European Patent Office
File 349:PCT FULLTEXT 1983-2002/UB=20020516,UT=20020509
         (c) 2002 WIPO/Univentio
?t s8/3,ae/1,3,4,6,7

 8/3,AE/1     (Item 1 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS
(c) 2002 European Patent Office. All rts. reserv.

00883153
USE OF GLIAL NEUROTROPHIC FACTOR (GDNF) FOR TREATMENT OF HEARING DISORDERS
VERWENDUNG DES GLIALEN, NEUROTROPHEN FAKTORS (GDNF) ZUR BEHANDLUNG VON
    GEHORSTORUNGEN
UTILISATION DU FACTEUR NEUROTROPHIQUE DERIVE DE CELLULES GLIALES (GDNF)
    POUR LE TRAITEMENT DES DEFICIENCES AUDITIVES
PATENT ASSIGNEE:
  Amgen Inc.,, (923239), One Amgen Center Drive, Thousand Oaks, California
    91320-1799, (US), (Proprietor designated states: all)
INVENTOR:
  MAGAL, Ella, 3022 Windrift Court, Thousand Oaks, CA 91360, (US)
LEGAL REPRESENTATIVE:
  Grunecker, Kinkeldey,  Stockmair & Schwanhausser Anwaltssozietat (100721)
    , Maximilianstrasse 58, 80538 Munchen, (DE)
PATENT (CC, No, Kind, Date):  EP 822829  A1  980211 (Basic)
                              EP 822829  B1  020102
                              WO 9730722  970828
APPLICATION (CC, No, Date):   EP 97906022 970214;  WO 97US2677  970214
PRIORITY (CC, No, Date): US 606176 960223; US 710219 960913
DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FI; FR; GB; GR; IE; IT; LI; LU;
  MC; NL; PT; SE
EXTENDED DESIGNATED STATES: AL; LT; LV; RO; SI
INTERNATIONAL PATENT CLASS: A61K-038/18
NOTE:
  No A-document published by EPO
LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:
Available Text  Language   Update    Word Count
      CLAIMS B  (English)  200201      451
      CLAIMS B   (German)  200201      379
      CLAIMS B   (French)  200201      476
      SPEC B    (English)  200201    17047
Total word count - document A           0
Total word count - document B       18353
Total word count - documents A + B  18353


 8/3,AE/3     (Item 2 from file: 349)
DIALOG(R)File 349:PCT FULLTEXT
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00397955
METHODS FOR TREATING MIDDLE AND INNER EAR DISORDERS
PROCEDES POUR LE TRAITEMENT DE TROUBLES DE L'OREILLE INTERNE ET MOYENNE
Patent Applicant/Assignee:
UNIVERSITY TECHNOLOGY CORPORATION,
MANNING Mark C,
SHEFTER Eli,
HART Michael J,
Inventor(s):
MANNING Mark C,
SHEFTER Eli,
HART Michael J,
Patent and Priority Information (Country, Number, Date):
Patent: WO 9738698 A1 **19971023**
Application: WO 97US6507 19970418 (PCT/WO US9706507)
Priority Application: US 9615572 19960418
Designated States: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN YU GH KE LS MW SD SZ UG AM AZ BY KG KZ MD RU TJ TM AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG
Publication Language: English
Fulltext Word Count: 4496

English Abstract
Provided are methods to deliver **drugs** to the middle or inner ear of a mammal in need of such **drug** comprising inserting a composition comprising a biocompatible polymer and at least one pharmacologically active agent. More particularly, the invention relates to a method for treating Meniere's disease using a composition of hyaluronic acid and gentamicin.

8/3,AE/4 (Item 3 from file: 349)
DIALOG(R)File 349:PCT FULLTEXT

00389979
USE OF GLIAL NEUROTROPHIC FACTOR (GDNF) FOR TREATMENT OF HEARING DISORDERS
UTILISATION DU FACTEUR NEUROTROPHIQUE DERIVE DE CELLULES GLIALES (GDNF) POUR LE TRAITEMENT DES DEFICIENCES AUDITIVES
Patent Applicant/Assignee:
AMGEN INC,
Inventor(s):
MAGAL Ella,
Patent and Priority Information (Country, Number, Date):
Patent: WO 9730722 A1 **19970828**
Application: WO 97US2677 19970214 (PCT/WO US9702677)
Priority Application: US 96606176 19960223; US 96710219 19960913
Designated States: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG UZ VN KE LS MW SD SZ UG AM AZ BY KG KZ MD RU TJ TM AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG
Publication Language: English
Fulltext Word Count: 19238

English Abstract
The present invention relates generally to methods for preventing and/or treating injury or degeneration of cochlear (and vestibular) hair cells and spiral ganglion neurons by administering glial cell line-derived neurotrophic factor (GDNF). The invention relates more specifically to methods for treating sensorineural hearing loss.

8/3,AE/6 (Item 5 from file: 349)

00377240

METHODS OF TREATING DISORDERS OF NON-VISUAL SENSORY EPITHELIA
PROCEDES DE TRAITEMENT DE TROUBLES DANS DES EPITHELIUMS SENSORIELS NON VISUELS

Patent Applicant/Assignee:
CAMBRIDGE NEUROSCIENCE INC,
UNIVERSITY OF VIRGINIA PATENT FOUNDATION,
E K SHRIVER CENTER FOR MENTAL RETARDATION,
MARCHIONNI Mark A,
MAHANTHAPPA Nagesh K,
SCHWARTING Gerald,
CORWIN Jeffrey,
Inventor(s):
MARCHIONNI Mark A,
MAHANTHAPPA Nagesh K,
SCHWARTING Gerald,
CORWIN Jeffrey,

Patent and Priority Information (Country, Number, Date):
Patent: WO 9717983 A1 **19970522**
Application: WO 96US18031 19961112 (PCT/WO US9618031)
Priority Application: US 956541 19951113
Designated States: AL AM AT AU AZ BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU IS JP KE KG KP KR KZ LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN KE LS MW SD SZ UG AM AZ BY KG KZ MD RU TJ TM AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG
Publication Language: English
Fulltext Word Count: 15055

English Abstract
In general, the present invention provides methods for promoting the function of inner ear cells using neuregulins. A novel aspect of the invention involves the use of neuregulins as growth factors to promote function of non-visual sensory epithelial cells. Trteating of the non-visual sensory epithelial cells to provide these effects may be achieved by contacting non-visual sensory epithelial cells with a polypeptide described herein. The treatments may be provided to slow or halt net cell loss or to increase the amount or quality of non-visual sensory epithelial tissue present in the vertebrate.

8/3,AE/7 (Item 6 from file: 349)

00292835

MULTI-FUNCTIONAL INNER EAR TREATMENT AND DIAGNOSTIC SYSTEM
SYSTEME MULTIFONCTIONNEL DE DIAGNOSTICS ET DE TRAITEMENTS DE L'OREILLE INTERNE

Patent Applicant/Assignee:
INNER EAR MEDICAL DELIVERY SYSTEMS INC,
Inventor(s):
ARENBERG Irving K,

Patent and Priority Information (Country, Number, Date):
Patent: WO 9510984 A1 **19950427**
Application: WO 94US11846 19941017 (PCT/WO US9411846)
Priority Application: US 93138827 19931018
Designated States: AU CA CN CZ FI JP KR NO NZ RU AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE
Publication Language: English
Fulltext Word Count: 30282

English Abstract

A therapeutic treatment apparatus (10) for use in the middle and inner ear. The apparatus (10) includes a tubular stem portion (14) attached to a **medicine** -retaining reservoir (30) with an internal cavity (38). The reservoir (30) includes multiple pores (46) therethrough or an opening (50) having a semipermeable membrane (54) therein which enables **medicine** delivery from the reservoir (30). Such delivery occurs when the reservoir (30) comes in contact with selected middle-inner ear interface tissues. A conductive member (70) for receiving electrical potentials from ear tissues is affixed to the apparatus (10). Alternatively, the apparatus (200) may include tubular first and second stem portions (204, 236) secured on opposite sides of a reservoir (220) along with a conductive member (270) attached thereto of the type indicated above.

8/3,AE,K/3 (Item 2 from file: 349)
DIALOG(R)File 349:PCT FULLTEXT

00397955
METHODS FOR TREATING MIDDLE AND INNER EAR DISORDERS
PROCEDES POUR LE TRAITEMENT DE TROUBLES DE L'OREILLE INTERNE ET MOYENNE
Patent Applicant/Assignee:
UNIVERSITY TECHNOLOGY CORPORATION,
MANNING Mark C,
SHEFTER Eli,
HART Michael J,
Inventor(s):
MANNING Mark C,
SHEFTER Eli,
HART Michael J,
Patent and Priority Information (Country, Number, Date):
Patent: WO 9738698 A1 **19971023**
Application: WO 97US6507 19970418 (PCT/WO US9706507)
Priority Application: US 9615572 19960418
Designated States: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN YU GH KE LS MW SD SZ UG AM AZ BY KG KZ MD RU TJ TM AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG
Publication Language: English
Fulltext Word Count: 4496

English Abstract
Provided are methods to deliver **drugs** to the middle or inner ear of a mammal in need of such **drug** comprising inserting a composition comprising a biocompatible polymer and at least one pharmacologically active agent. More particularly, the invention relates to a method for treating Meniere's disease using a composition of hyaluronic acid and gentamicin.

Patent and Priority Information (Country, Number, Date):
Patent: ... **19971023**
Fulltext Availability:
Detailed Description
Claims

English Abstract
Provided are methods to deliver **drugs** to the middle or inner ear of a mammal in need of such **drug** comprising inserting a composition comprising a biocompatible polymer and at least one pharmacologically active agent...
Publication Year: **1997**

Detailed Description
... to the inner ear tissue regions is typically through a variety of structures including the **round window** membrane, the oval window/stapes footplate and the annular ligament. For the purposes of this...

...various diseases and conditions associated with these and other inner ear tissues, the delivery of **medicines** is important. Exemplary **medicines** , or substances having biological or pharmacological activity, that are typically used to treat inner ear tissues include urea, mannitol, sorbitol, glycerol, xylocaine, epinephrine, immunoglobulins, sodium chloride, steroids, heparin, hyaluronidase, aminoglycoside **antibiotics** (e.g., streptomycin/gentamicin), and other **drugs** , biological materials, phan-naceutical compositions and therapeutic agents suitable for treating tissues of the human...

...and inner ears is hampered by the routes of administration currently

available. For example, typically **antibiotics** are systemically administered to treat infections of the middle ear. Systemic administration of **antibiotics** to combat middle ear infection generally results in a prolonged lag time to achieve therapeutic levels in the middle car, and requires high initial **doses** in order to achieve such levels. These drawbacks complicate the ability to obtain therapeutic levels and may preclude the use of some **antibiotics** altogether. Systemic
administration is most often effective when the infection has reached advanced stages, but damage may already have been done to the middle ear and inner ear structure.

Drugs also can be administered by injection or lavage to the middle ear, but such administration cannot generally be used to achieve prolonged therapeutic levels.

Similarly, ear **drops** can be used to apply **antibiotics** to the ear canal, but the ability of **antibiotics** to reach the middle ear when applied in this manner is difficult to predict or...

...g., regarding the possible ototoxic effects of penetration enhancers that may be used. Middle ear **drug** delivery is further complicated by the fact that the ciliary action of the cells lining the mucous membrane clears the middle ear of **medications** that do arrive.
Delivery of **drugs** to the inner ear is even more problematical. For example, in the case of Meniere...

...The current primary therapy for Meniere's patients, if change in diet and administration of **antibiotics** does not alleviate the symptoms, is a vestibular nerve section. By sectioning the vestibular nerve...

...days.

An alternative therapy is to inhibit vestibular function with an ototoxic therapeutic agent. Aminoglycoside **antibiotics** , such as gentamicin sulfate (GS), are I 0 known to be ototoxic, causing loss of hearing and vestibular function. However, with the appropriate **dose** , it should be possible to inhibit vestibular function without affecting hearing. If the **drug** is placed in the middle ear, which is accessible from the outside, the **drug** can diffuse through the round membrane and into the inner ear, which is very difficult to access. It is essential that **drug** remain in contact with the round 1 5 membrane for all of the **dose** to be delivered.

Clinical studies for treating Meniere's disease have been performed using GS...via percolation back through the eardrum, if administered intertympanically. These problems lead to variation in **dose** , often requiring additional treatments, which increase the chance of hearing loss. Consequently, GS treatment to treat Meniere's disease has met with limited acceptance. Development of a **dosage** form which could reliably deliver a fixed **dose** and remain in contact with the round membrane would be highly advantageous for solving this and other problems relating to delivering **drugs** to the middle and inner ears.

Clearly what is needed is a method to deliver therapeutically effective levels of **drug** to sufferers of diseases and other conditions of the middle or inner ear, in a...

...More specifically, the present invention provides a gel composition system and methods for delivering a **drug** or other therapeutic, e.g., GS, to the middle or inner ear in a more...

...200 mg per patient and, even more specifically, about 40 mg per patient. If the **doses** are greater than 200 mg, the patient should be **dosed** more than once. Those skilled in the art can determine optimal **doses** and **dosage** schedules.

The gel component of the system may comprise hyaluronic acid. Hyaluronic acid ("HA") is...of about three million. It can be purchased from Phannacia.

HealonTMcan be impregnated with high **doses** of GS (equivalent to loads of up to 200 mg/ml of gentarnicin base, corresponding...

...days with minimal agitation. Consequently, the GS/sodium hyaluronic acid composition may provide a superior **dosage** form for nonsurgical treatment for unilateral vestibular dysfunction and other disorders of the middle and inner ears.

The **drug** delivery composition may include the following.

I . HA solutions in which a **drug** substance is dissolved or dispersed;
2. A cross-linked HA gel forming a macromolecular "cage" in which a **drug** substance is dispersed so long as cross-linking does not make the polymer rigid;
3...

...linked mixed gel of HA and at least one other hydrophific polymer in which a **drug** substance is dispersed;
4. A cross-linked gel of HA or cross-linked mixed gel of HA and at least I 0 one other hydrophilic polymer containing a **drug** substance which is covalently attached to the macromolecules of HA or the other polymer.

Such...substance which has biological or pharmacological activity and which is normally considered to be a **drug** or other therapeutic can be used as the **drug** component in the composition according to the present invention. Exemplary substances are set forth above. The terms " **drug** " and " **drug** substance" are also used herein to describe such substances. The substances can be soluble or...

...above, HA is the preferred polymeric component of the composition which controls release of the **drug** . Other biocompatible polymers may also be used including celluloses, gelatins, Pluronics, Tetronics, the latter two...

...mucopolysaccharides (e.g., glycosaminoglycans) and other biocompatible polymers having characteristics similar to HA.

When a **drug** substance is dissolved or dispersed in the biocompatible polymer, its diffusion is substantially slower than...

...proper-ties of the system. Without being bound by theory, in the case of a **drug** containing cationic groups, an ionic interaction can occur between HA macromolecules having carboxyl groups and the **drug** and this interaction slows down the diffusion of the **drug** from the system even further.

The HA concentration in the products, based on the soluble...

...to 4% by wt. and higher, depending on the end use of the product. The **drug** concentration can be varied over very broad limits and preferably should be chosen depending upon the solubility of the **drug** , its pharmacological activity, the desirable effect of the end product, patient size, weight and so...

...all factors known to those skilled in the art. Although many of the above-discussed **medicines** can already be used as injectables, the products according to the invention containing non-soluble HA are substantially more efficient as injectable **drug** delivery systems for use in methods of treating the middle and inner ears.

In a...PBS at the various time points. Amounts are given as the

percentage of the total **dose** of GS. For a typical release study, the loading factor is 200 mg of gentarnicin...but the kinetics do not change if the receiver volume is doubled. Therefore, the total **dose** is 64 mg of GS, which has been found to be effective for inhibition of...

...Goosen el al. (Zhang, X., Wyss, U.P., Pichora, D., Goosen, M.F.A. "Biodegradable **controlled antibiotic release** devices for osteomyclitis: optimization of release properties." J Pharm. Pharmacol. 46 (1994) 718) The two methods are in excellent agreement (see below).

The target **dose** for these studies is taken to be approximately 64 mg of GS. As the volume of the middle ear is limited, and to allow the administration of the **drug** to be as convenient as possible. the total **dose** is loaded into 0.2 ml of sodium hyaluronate gel. The middle ear accommodates volumes up to 0.8 ml.

Example I - **Control Release** Studigs. Initial **release** studies are performed into PBS, a common receiver fluid for **controlled release** studies. The **release** kinetics are well **controlled** and reproducible over the first four hours. There appears to be a small burst effect from **drug** adsorbed to the surface of the gel, but it is much less than non-nally...

...other biodegradable polymers. Steady-state release is rapidly established. By four hours, much of the **drug** is released (50-60%), and the rate of release begins to slow. The **drug** is nearly completely delivered (-75%) by 24 hours.

The variability is very small, with a...

...The kinetic profile is approximately the same as in PBS, except that the amount of **drug** released in a given time is slightly lower (-90% of the level for release into nature of the **controlled release** properties of this system, the 1 5 rate of initial release is examined carefully. Monitoring...

...very little burst effect, even at 200 mg/ml, indicating that very little of the **drug** is adsorbed to the surface of the gel.

Comparison of the data to the previous...

...more often. The composition is always somewhat fluid, unlike solid implants or microspheres or other **controlled release dosage** forms. This mobility means that agitation of the gel surface will be more disruptive than...

Claim

I . A method for delivering a **medicine** to the inner ear of a mammal in need of such **medicine** comprising inserting into the middle ear a composition comprising a biocompatible polymer and at least...

...according to Claim 1, wherein said substance having biological or pharmacological activity is an arninoglycoside **antibiotic** .

4 A method according to Claim 3, wherein said substance having biological or pharmacological activity...

...in Claim I 1, wherein the substance having biological or pharmacological activity is an aminoglycoside **antibiotic** .

14 The use of the combination of materials as recited in Claim I 1, wherein...

?

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?ds

Set     Items   Description
S1        160   ROUND()WINDOW? OR RWM
S2      53043   (CONTROL? OR DELAY? OR SUSTAIN?)(3N)(DELIVER? OR RELEASE? -
             OR TARGET?)
S3     571544   DRUG? OR MEDICATION? OR MEDICINE? OR ANTIBIOTIC? OR DOSAGE?
              OR DOSE? OR DROPS? OR MEDICINAL? OR PHARMACEUTIC? OR REMEDY -
             OR REMEDIES OR MEDICINAL? OR MEDICANT?
S4         11   S1 (5N)2
S5          7   S1 AND S3
S6          2   S1 AND S2 AND S3
S7          1   S1 (5N) S3
?show files
File 350:Derwent WPIX 1963-2001/UD,UM &UP=200232
         (c) 2002  Thomson Derwent
File 344:CHINESE PATENTS ABS APR 1985-2002/APR
         (c) 2002 EUROPEAN PATENT OFFICE
File 347:JAPIO Oct/1976-2001/Dec(Updated 020503)
         (c) 2002 JPO & JAPIO
File 371:French Patents 1961-2002/BOPI 200209
         (c) 2002 INPI.  All rts. reserv.
```

?t s5/9/4,5,6,7

5/9/4 (Item 4 from file: 350)
DIALOG(R)File 350:Derwent WPIX

014051143
WPI Acc No: 2001-535356/200159
Related WPI Acc No: 2001-217695
XRAM Acc No: C01-159388

Prevention or reversal of hearing loss by administration of an antioxidant compound

Patent Assignee: HENDERSON D (HEND-I); HOFFER M E (HOFF-I); KOPKE R D (KOPK-I)
Inventor: HENDERSON D; HOFFER M E; KOPKE R D
Number of Countries: 001 Number of Patents: 001
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
US 20010007871	A1	20010712	US 9769761	A	19971216	200159	B
			US 98126707	A	19980731		
			US 2001766625	A	20010123		

Priority Applications (No Type Date): US 9769761 P 19971216; US 98126707 A 19980731; US 2001766625 A 20010123
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
US 20010007871	A1		19	A61K-038/00	Provisional application US 9769761
					CIP of application US 98126707
					CIP of patent US 6177434

Abstract (Basic): US 20010007871 A1

NOVELTY - A method of reducing, restoring or protecting hearing loss comprises administering an antioxidant compound such as adenosine agonist, trophic factor, NMDA antagonist or steroid to the patient.

ACTIVITY - Auditory.

MECHANISM OF ACTION - Adenosine agonist; NMDA antagonist.

USE - For preventing and/or reversing sensorineural hearing loss (SNHL) or noise/toxin-induced hearing loss.

ADVANTAGE - The compound upregulates antioxidant enzyme activity. The treatment differs from hearing protection devices in that it does not need to be worn and does not decrease hearing acuity as hearing protectors do. The treatment has the potential to reverse the hearing loss after it has occurred.

pp; 19 DwgNo 0/12

Extension Abstract:

SPECIFIC COMPOUNDS - 6 Specific compounds are claimed e.g. dexamethasone (Ia):

ADMINISTRATION - The compound is administered systemically, intravenously, orally or topically. The topical administration is through a catheter to the **round window** membrane of the inner ear.

EXAMPLE - An army infantryman suffering from moderate to severe hearing loss was treated with an initial **dose** of L-N-acetyl cysteine (LNAC) (70 mg/kg) by mouth followed by LNAC (35 mg/kg) by mouth QID for seven days. The soldier's hearing recovered after administration of the agent. The degree of hearing recovery was greater than usually seen with this degree of hearing impairment due to noise.

Title Terms: PREVENT; REVERSE; HEARING; LOSS; ADMINISTER; ANTIOXIDANT; COMPOUND
Derwent Class: B05
International Patent Class (Main): A61K-038/00
International Patent Class (Additional): A61K-031/52; A61K-031/56
File Segment: CPI
Manual Codes (CPI/A-N): B01-B03; B04-B03A; B10-B02J; B14-N02
Chemical Fragment Codes (M2):
01 D011 D019 D931 F012 F013 F014 F015 F113 G010 G100 H1 H102 H122 H2

H201 H4 H403 H422 H481 H8 L943 M280 M311 M313 M321 M331 M342 M373 M392 M412 M431 M511 M521 M531 M540 M782 M904 M905 P921 RA563Y-K RA563Y-M

Chemical Fragment Codes (M5):
02 M431 M782 M904 M905 M910 P921 R00002-K R00002-M R14648-K R14648-M
03 M431 M782 M904 M905 M910 P921 R00496-K R00496-M

Derwent Registry Numbers: 0002-U; 0496-U
Specific Compound Numbers: RA563Y-K; RA563Y-M
Key Word Indexing Terms:
01 449791-1-0-0-CL 88752-2-0-0-CL 100837-1-0-0-CL 449790-1-0-0-CL

5/9/5 (Item 5 from file: 350)

013733465 **Image available**
WPI Acc No: 2001-217695/200122
Related WPI Acc No: 2001-535356
XRAM Acc No: C01-064863

Reducing, restoring or protecting against hearing loss comprises oral or topical administration of antioxidants e.g. R-N6-phenylisopropyl adenosine (R-PIA), L-N-acetylcysteine (L-NAC) or glutathione monoethyl ester

Patent Assignee: US SEC OF NAVY (USNA)
Inventor: HENDERSON D; HOFFER M E; KOPKE R D
Number of Countries: 001 Number of Patents: 001
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
US 6177434	B1	20010123	US 9769761	A	19971216	200122	B
			US 98126707	A	19980731		

Priority Applications (No Type Date): US 9769761 P 19971216; US 98126707 A 19980731
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
US 6177434	B1		16	A61K-031/52	Provisional application US 9769761

Abstract (Basic): US 6177434 B1

NOVELTY - Reducing, restoring or protecting against hearing loss by administering antioxidants (I) is new.

ACTIVITY - Auditory.

MECHANISM OF ACTION - The compounds are adenosine agonists, acadesine or adenosine deaminase inhibitors and augment inner ear antioxidant defenses such as adenosine agonists which reduce inner ear cochlear hair cell loss or up regulate agents which increase inner ear glutathione levels. They also upregulating antioxidant enzyme activity, curtail programmed cell death pathways and induce/enhance cell repair mechanisms in the inner ear.

USE - For reducing, restoring or protecting against hearing loss and sensorineural hearing loss, particularly caused by inner ear damage due to noise or toxins such as chemotherapeutic agents e.g. cisplatin and the aminoglycoside **antibiotics** e.g. gentamycin.

ADVANTAGE - The method differs form use of mechanical noise attenuators to hearing protection devices since it does not need to be worn or devices and does not decrease hearing acuity as hearing protectors do. The method also has the potential to reverse sensorineural hearing loss or toxic hearing loss after it has occurred. Administration of the adenosine agonists topically by means of a catheter to the **round window** membrane avoids the side-effects associated with systemic administration of these **drugs** e.g. hypotension, cardiac depression, hypothermia and crossing of the blood labyrinthine barrier.

DESCRIPTION OF DRAWING(S) - The figure shows a comparison of the speech reception threshold values of an individual who suffered an idiopathic sensorineural hearing loss before and after administration

of a topical rescue agent and depicts the complete recovery of the profoundly elevated speech reception threshold back to normal level.
pp; 16 DwgNo 1/12

Technology Focus:

TECHNOLOGY FOCUS - **PHARMACEUTICALS** - (I) is R-N6-phenylisopropyl adenosine (R-PIA), L-N-acetylcysteine (L-NAC) or glutathione monoethyl ester, preferably R-PIA and (I) upregulates antioxidant enzyme activity. (I) can also be 1-2-oxothiazolidine-4-carboxylic acid (Procysteine

Extension Abstract:

ADMINISTRATION - (I) is administered orally or topically (preferably through a catheter to the **round window** membrane of the inner ear). The agents may be applied before, during or after noise trauma or toxin exposure.

EXAMPLE - A patient with sudden severe onset hearing loss and tinnitus in his right ear was initially given conventional therapy consisting of oral prednisone over 10 days. He showed had no response to this treatment and three weeks after experiencing the hearing loss he was treated with topically administered methylprednisilone at a concentration of 125 mg/ml. A **round window** micro-catheter was preloaded with 0.125 ml of the compound after the catheter was secure in the **round window** niche. The catheter was then attached to a pump which pumped the methylprednisiolne into the catheter at 10 microliters per hour over 14 days. The patient experienced a complete recovery of his profoundly impaired elevated speech reception and a complete recovery of his profoundly impaired word discrimination ability. The patient's tinnitus was also completely resolved following treatment.

A 10-4M solution of R-PIA was placed on the **round window** membrane of one ear of chinchillas for 30 minutes and saline was placed as a control on the **round window** of the other year. After 30 minutes the fluids were removed, the surgical sites were closed and the animals were exposed to 4 kHz octave band noise at 105 dB SPL for 30 minutes. The animals had hearing thresholds measured at various frequencies at days 0, 1, 2, 4 and 20 after the noise treatment using evoked potentials measured from the inferior colliculus. R-PIA treated ears showed a faster and more complete recovery of hearing thresholds than ears treated with saline. There was significantly less permanent hearing threshold shift in R-PIA treated ears compared with compared to saline treated ears at 4, 8 and 16 kHz.

Title Terms: REDUCE; RESTORATION; PROTECT; HEARING; LOSS; COMPRISE; ORAL; TOPICAL; ADMINISTER; ANTIOXIDANT; ADENOSINE; PIA; N; GLUTATHIONE; ESTER

Derwent Class: B02; B05

International Patent Class (Main): A61K-031/52

International Patent Class (Additional): A01N-043/78; A01N-043/90; A61K-031/195; A61K-031/425

File Segment: CPI

Manual Codes (CPI/A-N): B04-B03; B04-C01A; B06-D09; B07-F01; B10-B02D; B11-C04B; B12-M02B; B14-D07; B14-L01; B14-N02; B14-S08

Chemical Fragment Codes (M1):

01 M423 M431 M782 M905 P921 RA3ITX-K RA3ITX-M

Chemical Fragment Codes (M2):

02 D011 D019 D931 F012 F013 F014 F015 F113 G010 G100 H1 H102 H122 H2 H201 H4 H403 H422 H481 H8 K0 L8 L812 L821 L834 L943 M280 M311 M313 M321 M331 M342 M373 M392 M412 M431 M511 M521 M531 M540 M782 M904 M905 P616 P921 R22995-K R22995-T R22995-M

03 H4 H498 H9 J0 J012 J1 J171 J3 J371 M210 M211 M262 M281 M312 M321 M332 M343 M349 M381 M391 M416 M431 M620 M782 M904 M905 P921 R04369-K R04369-M

04 F012 F014 F710 J0 J011 J1 J111 J5 J521 L9 L922 M280 M320 M413 M431 M510 M521 M530 M540 M782 M904 M905 P921 R03934-K R03934-M

Specific Compound Numbers: RA3ITX-K; RA3ITX-M

Key Word Indexing Terms:

01 96259-1-0-0-CL 103869-1-0-0-CL 12143-0-0-0-CL 103020-0-0-0-CL

5/9/6 (Item 6 from file: 350)

013293165 **Image available**
WPI Acc No: 2000-465100/200040
XRAM Acc No: C00-139926
XRPX Acc No: N00-347179

Delivery of therapeutic agents into inner ear comprising placing drug **delivery device containing sustained release therapeutic agent into** round window **niche of subject, where agent contacts window membrane and passes into inner ear**

Patent Assignee: DURECT CORP (DURE-N)
Inventor: ARENBERG I K; ARENBERG M H; BERGLUND J A; LEMKE C; THEEUWES F
Number of Countries: 091 Number of Patents: 003
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
WO 200033775	A1	20000615	WO 99US28716	A	19991203	200040	B
AU 200021646	A	20000626	AU 200021646	A	19991203	200045	
EP 1133269	A1	20010919	EP 99965987	A	19991203	200155	
			WO 99US28716	A	19991203		

Priority Applications (No Type Date): US 98205251 A 19981204
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
WO 200033775	A1	E	62	A61F-011/00	
AU 200021646	A			A61F-011/00	Based on patent WO 200033775
EP 1133269	A1	E		A61F-011/00	Based on patent WO 200033775

Designated States (National): AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
Designated States (Regional): AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
Designated States (Regional): AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI

Abstract (Basic): WO 200033775 A1

NOVELTY - A method for delivery of therapeutic agents into the inner ear of a subject over time comprises placing at least a portion of a **drug** delivery unit into a **round window** niche of the subject, where the **drug** delivery unit comprises at least one synthetic carrier media material, at least one cross-linked carrier media material or at least one sustained release synthetic carrier medium, and at least one therapeutic agent, and the therapeutic agent contacts and passes through the **round window** membrane and enters the inner ear.

ACTIVITY - Auditory.

USE - For delivery of **drugs** into the inner ear (claimed), particularly in treatment of endolymphatic hydrops, endolymphatic hypertension, perilymphatic hypertension, perilymphatic hydrops, perilymphatic fistula, intracochlear fistula, Meniere's disease, tinnitus, vertigo, hearing loss related to hair cell or ganglion cell damage or malfunction and ear membrane ruptures.

ADVANTAGE - The process allows controlled **drug** delivery with easy termination of therapy if required.

DESCRIPTION OF DRAWING(S) - The figure shows the schematic cross-sectional view of the **drug** delivery unit positioned within the **round window** niche.

Ear canal (5)
Drug delivery unit (10)
Soft or semi-soft mass (12)
Controlled release carrier material (14)
Therapeutic agent (16)
Ear (40)
Round window niche (42)
Inner ear (44)
Round window membrane (46)

Middle ear (50)
Interior side wall (54)
Main opening (56)
Tympanic membrane (60) and
Incision (62).
pp; 62 DwgNo 2/8
Technology Focus:
TECHNOLOGY FOCUS - **PHARMACEUTICALS** - Preferred Delivery Unit: The agent may be transferred to the membrane from a fluid reservoir via a wick
Extension Abstract:
ADMINISTRATION - No **dosage** given. Administration is auditory.
EXAMPLE - None given
Title Terms: DELIVER; THERAPEUTIC; AGENT; INNER; EAR; COMPRISE; PLACE; **DRUG** ; DELIVER; DEVICE; CONTAIN; SUSTAINED; RELEASE; THERAPEUTIC; AGENT; ROUND; WINDOW; NICHE; SUBJECT; AGENT; CONTACT; WINDOW; MEMBRANE; PASS; INNER; EAR
Derwent Class: B07; P32
International Patent Class (Main): A61F-011/00
International Patent Class (Additional): A61K-009/00
File Segment: CPI; EngPI
Manual Codes (CPI/A-N): B11-C03; B11-C04; B12-M10; B14-N02
Chemical Fragment Codes (M6):
01 M905 P921 R051 R052 R111 R150 R170 R251 R501 R532 R760

5/9/7 (Item 7 from file: 350)
DIALOG(R)File 350:Derwent WPIX

010268751 **Image available**
WPI Acc No: 1995-170006/199522
XRPX Acc No: N95-133302
Multi function inner ear treatment and diagnosis probe - has porous reservoir for medicines **connected to tubular stem with electrical conductor for ECoG potentials**
Patent Assignee: INNER EAR MEDICAL DELIVERY SYSTEMS INC (INNE-N)
Inventor: ARENBERG I K
Number of Countries: 028 Number of Patents: 007
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
WO 9510984	A1	19950427	WO 94US11846	A	19941017	199522	B
US 5421818	A	19950606	US 93138827	A	19931018	199528	
AU 9480817	A	19950508	AU 9480817	A	19941017	199533	
US 5474529	A	19951212	US 93138827	A	19931018	199604	
			US 95426215	A	19950421		
US 5476446	A	19951219	US 93138827	A	19931018	199605	
			US 95426190	A	19950421		
EP 724408	A1	19960807	EP 94931900	A	19941017	199636	
			WO 94US11846	A	19941017		
AU 682908	B	19971023	AU 9480817	A	19941017	199750	

Priority Applications (No Type Date): US 93138827 A 19931018; US 95426215 A 19950421; US 95426190 A 19950421
Cited Patents: US 5037380; US 5219334; US 5281287; US 5286254; US 5304134
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
WO 9510984	A1	E	110	A61B-017/36	
Designated States (National): AU CA CN CZ FI JP KR NO NZ RU					
Designated States (Regional): AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE					
US 5421818	A		28	A61M-025/00	
AU 9480817	A			A61B-017/36	Based on patent WO 9510984
US 5474529	A		27	A61M-025/00	Div ex application US 93138827 Div ex patent US 5421818
US 5476446	A		27	A61M-025/00	Div ex application US 93138827

Div ex patent US 5421818

EP 724408 A1 E 1 A61B-017/36 Based on patent WO 9510984

Designated States (Regional): AT BE CH DE DK ES FR GB IE IT LI LU NL PT SE

AU 682908 B A61F-011/00 Previous Publ. patent AU 9480817
Based on patent WO 9510984

Abstract (Basic): WO 9510984 A

The device (10) delivers therapeutic agents to the middle and inner ear. It has a tubular stem (14) joined to a **medicine** reservoir (30), permitting fluid transfer through its walls. The fluid, or **medicine** , may be transferred by multiple pores (46), or via a semi-permeable membrane, in contact with middle-inner ear tissue. The stem passage may include a valve.

Part of the device may be radiopaque, visible to X rays. An electrical conductor (70), fixed to the device, may carry potentials in and out of the inner ear. The conductor may have a spherical end (86), for electrocochleography. The reservoir may have a double wall and the stem may have an inflatable section, pressurising the reservoir.

USE/ADVANTAGE - Therapeutically testing, treating and/or analysing conditions of ear by delivering medicaments, withdrawing fluids, changing fluid temperature, pressure and volume, in inner ear.

Dwg.1/15

Abstract (Equivalent): US 5476446 A

A treatment apparatus for delivering therapeutic agents into the inner ear of a human subject comprising:

a reservoir portion comprising an exterior wall and an internal cavity in it surrounded by the wall;

a tubular first stem portion comprising an open first end, a second end, and a passageway extending continuously through the first stem portion, the second end of the first stem portion being connected to the reservoir portion so that the passageway through the first stem portion is in fluid communication with the internal cavity in the reservoir portion; and

a tubular second stem portion comprising an open first end, a second end, and a passageway extending continuously through the second stem portion, the second end of the second stem portion being connected to the reservoir portion so that the passageway through the second stem portion is in fluid communication with the internal cavity in the reservoir portion.

Dwg.11/15

US 5474529 A

The probe comprises a first reservoir with an exterior wall and an internal cavity surrounded by wall, a tubular first stem portion comprising a first and second end, and a passageway extending continuously through first and second end of said first stem portion being connected to said first reservoir portion so that said passageway through said first stem portion is in fluid communication with said internal cavity in said first reservoir portion, a tubular second stem portion comprising a first and second end, and a passageway extending continuously through said second stem portion, said second end of said second stem portion being connected to said first reservoir portion so that said passageway through said second stem portion is in fluid communication with said internal cavity in said first reservoir portion.

A second reservoir portion comprising an exterior wall and an internal cavity therein surrounded by said wall of said second reservoir portion, said first end of said first stem portion being connected to said second reservoir portion so that said passageway through said first stem portion is in fluid communication with said internal cavity in said second reservoir portion and at least one tubular additional stem portion.

Dwg.12/15

US 5421818 A

The apparatus (10) includes the reservoir (30) which consists of front, rear and blunt end portions. The blunt end portion consists of a continuous, uninterrupted exterior surface with the reservoir also

having an exterior wall surrounding an internal cavity (38). Fluids pass through the porous wall of the reservoir which has an opening with a semi-permeable membrane across it. The tubular stem (14) has an open first end (20), a second end (22) connected to the reservoir and a passageway (24) which extends through the stem.

The passageway communicates fluids with the internal cavity in the reservoir and a valve is located within the passageway. At least part of the apparatus is radiopaque and visible when X-rays are applied. An elongated conductor attached to the reservoir wall transmits electrical potentials into and out of the inner ear. The **medicine** is delivered through the external auditory canal of the ear and into the **round window** membrane within the middle ear where it diffuses into the inner ear.

ADVANTAGE - Controlled, repeatable and uniform delivery to selected ear tissue regions. Compact size permits insertion using minimally-invasive microsurgery. Easily supplied with **medicine** while inserted in ear.

Dwg.2/15

Title Terms: MULTI; FUNCTION; INNER; EAR; TREAT; DIAGNOSE; PROBE; POROUS; RESERVOIR; **MEDICINE** ; CONNECT; TUBE; STEM; ELECTRIC; CONDUCTOR; POTENTIAL

Derwent Class: P31; P32; P34; S05

International Patent Class (Main): A61B-017/36; A61F-011/00; A61M-025/00

File Segment: EPI; EngPI

Manual Codes (EPI/S-X): S05-M

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09/205,251

FILE 'HCAPLUS' ENTERED AT 10:02:29 ON 21 MAY 2002
L13 39257 S (CONTROL? OR DELAY? OR SUSTAIN?) (3A) (DELIVER? OR RELEASE? O
L14 155 S ROUND()WINDOW?
L15 1458586 S DRUG? OR MEDICATION? OR MEDICINE? OR ANTIBIOTIC? OR DOSAGE? O
L16 0 S L13 AND S14 AND S15
L17 69 S L14 AND L15
L18 29 S L14/TI,ID
L19 15 S L18 AND L15

=> d l19 iall 1-15

L19 ANSWER 1 OF 15 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:852343 HCAPLUS
TITLE: Hearing Loss in Relation to **Round Window** Membrane Morphology in Experimental Chronic Otitis media
AUTHOR(S): Nordang, Leif; Anniko, Matti
CORPORATE SOURCE: Department of Otorhinolaryngology and Head and Neck Surgery, University Hospital (Akademiska sjukhuset), Uppsala, Swed.
SOURCE: ORL (2001), 63(6), 333-340
CODEN: ORLJAH; ISSN: 0301-1569
PUBLISHER: S. Karger AG
DOCUMENT TYPE: Journal
LANGUAGE: English
CLASSIFICATION: 14 (Mammalian Pathological Biochemistry)
ABSTRACT:
The present study was performed to test the effect of single and repeated Pseudomonas aeruginosa exotoxin A (PaExoA) instillations in the middle ear of the rat. The hearing level was examd. by the ABR technique, round window membrane (RWM) thickness was measured and morphol. was studied by light microscopy. The results showed both reversible and permanent hearing loss (HL). In animals that received a single **dose** of PaExoA, the RWM thickness doubled initially and remained thickened during the observation period. When PaExoA was instilled on several occasions, RWM thickness doubled, before decreasing to near-control levels. This study confirms the toxicity of PaExoA and the partially reversible HL occurring after a single application of the toxin. The diminished effect of repeated toxin instillations - despite the

decreasing thickness of the RWM - is discussed.

REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD.
REFERENCE(S): (1) Alzamil, K; Ann Otol Rhinol Larnygol 2000, V109, P30 MEDLINE
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(3) Demaria, T; Acta Otolaryngol (Stockh) 1999, V119, P583 HCAPLUS
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L19 ANSWER 2 OF 15 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:839201 HCAPLUS
DOCUMENT NUMBER: 136:160895
TITLE: Microdose gentamicin administration via the **Round Window** Microcatheter: results

in patients with Meniere's disease

AUTHOR(S): Hoffer, Michael E.; Kopke, Richard D.; Weisskopf, Peter; Gottshall, Kim; Allen, Keith; Wester, Derin

CORPORATE SOURCE: The Department of Defense Spatial Orientation Center, Naval Medical Center San Diego, San Diego, CA, 93124, USA

SOURCE: Annals of the New York Academy of Sciences (2001), 942(Vestibular Labyrinth in Health and Disease), 46-51

CODEN: ANYAA9; ISSN: 0077-8923

PUBLISHER: New York Academy of Sciences

DOCUMENT TYPE: Journal

LANGUAGE: English

CLASSIFICATION: 1-5 (Pharmacology)
Section cross-reference(s): 63

ABSTRACT:

Transtympanic gentamicin is becoming increasingly popular in the treatment of Meniere's disease. In this report we examine our experience with the use of microdose gentamicin via the Round Window Microcatheter for the treatment of Meniere's disease. Thirty-six patients were treated with gentamicin administration via the Round Window Microcatheter between July 1997 and August 2000. The patients all underwent 10 days of continuous treatment with a total ***dose*** of 2.4-3.75 mg of gentamicin (10 mg/mL). All patients had extensive pre-, intra-, and post-therapy auditory and vestibular testing. In this group, vertigo was eliminated in 89% of the patients, and tinnitus and pressure were significantly reduced in over 60% of the patients. Only one patient suffered a significant hearing loss and, most importantly, in all but one patient vestibular function was improved or normalized after treatment. Round Window Microcatheter-administered microdose gentamicin is an exciting new treatment for Meniere's disease. Preliminary results indicate that vertigo can be controlled without a significant redn. in cochlear or vestibular function in most patients. These results suggest that this therapy may be acting at a non-hair cell site. Our results are compared to the published literature examg. transtympanic injection. In addn., the underlying science supporting this type of treatment is examd.

09/205,251

SUPPL. TERM: microdose gentamicin sustained release round window microcatheter Meniere's disease

INDEX TERM: Ear
(Meniere's disease; microdose gentamicin via the Round Window Microcatheter in humans with Meniere's disease)

INDEX TERM: Medical goods
(catheters, Round Window Microcatheter; microdose gentamicin via the Round Window Microcatheter in humans with Meniere's disease)

INDEX TERM: **Drug** delivery systems
(injections, sustained release, microdosage through Round Window Microcatheter; microdose gentamicin via the Round Window Microcatheter in humans with Meniere's disease)

INDEX TERM: Human
(microdose gentamicin via the Round Window Microcatheter in humans with Meniere's disease)

INDEX TERM: 1403-66-3, Gentamicin
ROLE: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(microdose gentamicin via the Round Window Microcatheter in humans with Meniere's disease)

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD.

REFERENCE(S):

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L19 ANSWER 3 OF 15 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:474604 HCAPLUS
DOCUMENT NUMBER: 136:210154
TITLE: **Round window** membrane delivery of L-methionine provides protection from cisplatin ototoxicity without compromising chemotherapeutic efficacy
AUTHOR(S): Li, Geming; Frenz, Dorothy A.; Brahmblatt, Sapna; Feghali, Joseph G.; Ruben, Robert J.; Berggren, Diana; Arezzo, Joseph; Van De Water, Thomas R.
CORPORATE SOURCE: Department of Otolaryngology, Albert Einstein College of Medicine, Bronx, NY, USA
SOURCE: Neurotoxicology (2001), 22(2), 163-176
CODEN: NRTXDN; ISSN: 0161-813X
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
CLASSIFICATION: 1-6 (Pharmacology)
ABSTRACT:

Cisplatin (cis-diamminedichloroplatinum(II) (CDDP)) is a widely used, highly effective, oncolytic agent that has serious ototoxic side-effects. To test the effectiveness of local delivery of L-methionine (L-Met) as an otoprotective agent against CDDP ototoxicity, we used a rat model of a highly metastatic breast cancer tumor, i.e. Fisher 344 rats implanted with MTLn3 breast cancer cells. Four exptl. groups were evaluated - I: untreated; II: CDDP-treated (three **dosages**); III: systemically-delivered L-Met + CDDP-treated; IV: locally delivered L-Met + CDDP-treated. The integrity of the outer hair cells (OHCs) was detd. using SEM (SEM); hearing was assessed by recording auditory brainstem responses (ABRs) at multiple frequencies. The chemotherapeutic effectiveness of CDDP was quantified by measuring changes in tumor mass and the presence of tumor metastasis. L-Met provided otoprotection of the OHCs against CDDP toxicity in the cochleae of rats following either systemic (III) or local (IV) administration. The ABRs were unchanged in each

of the L-Met protection Groups (III and IV) and in the untreated animals of Group I. Treatment with CDDP only (II) induced significant hearing losses at
both 16 and 18 kHz when compared to ABRs of untreated rats(I). CDDP was effective in controlling the MTLn3 initiated breast cancer tumors in the CDDP-treated (II) and the local L-Met protection, CDDP-treated (IV) Groups. In
contrast, the tumors in the systemic L-Met protection, CDDP-treated Group (III)
were not controlled by the CDDP treatment regime. This study demonstrates that
local delivery of L-Met to the scala tympani of the cochlea via the round window membrane (IV) provides effective protection against CDDP ototoxicity without compromising its ability to control a highly metastatic form of cancer.

SUPPL. TERM: cisplatin ototoxicity metastatic cancer methionine
INDEX TERM: Antitumor agents
(metastasis; round window membrane delivery of L-methionine provides protection from cisplatin ototoxicity without compromising chemotherapeutic efficacy)
INDEX TERM: Ear
(tectorial membrane; round window membrane delivery of
L-methionine provides protection from cisplatin ototoxicity without compromising chemotherapeutic efficacy)
INDEX TERM: Ear
(tympanic membrane; round window membrane delivery of L-methionine provides protection from cisplatin ototoxicity without compromising chemotherapeutic efficacy)
INDEX TERM: 15663-27-1, Cisplatin
ROLE: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(round window membrane delivery of L-methionine provides
protection from cisplatin ototoxicity without compromising chemotherapeutic efficacy)
INDEX TERM: 63-68-3, L-Methionine, biological studies
ROLE: PAC (Pharmacological activity); THU (Therapeutic use);
BIOL (Biological study); USES (Uses)
(round window membrane delivery of L-methionine provides
protection from cisplatin ototoxicity without compromising chemotherapeutic efficacy)

09/205,251

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L19 ANSWER 4 OF 15 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:307910 HCAPLUS
DOCUMENT NUMBER: 135:3522
TITLE: Quantification of solute entry into cochlear perilymph through the **round window** membrane
AUTHOR(S): Salt, Alec N.; Ma, Yilong
CORPORATE SOURCE: Department of Otolaryngology, Washington University School of Medicine, St. Louis, MO, 63110, USA
SOURCE: Hearing Research (2001), 154(1-2), 88-97
CODEN: HERED3; ISSN: 0378-5955
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
CLASSIFICATION: 13-6 (Mammalian Biochemistry)
Section cross-reference(s): 1, 63

ABSTRACT:
The administration of **drugs** to the inner ear via the round window membrane is becoming more widely used for both clin. and exptl. purposes. The actual **drug** levels achieved in different regions of the inner ear by this method were not established. The present study has made use of simulations of solute movements in the cochlear fluids to describe the distribution of a marker solute in the guinea pig cochlear fluid spaces. Simulation parameters were derived from exptl. measurements using a marker ion, trimethylphenylammonium (TMPA). The distribution of this ion in the cochlea was monitored without vol. disturbance using TMPA-selective microelectrodes sealed into the 1st and second turns of scala tympani (ST). TMPA was applied to perilymph by irrigation of the intact round window membrane with 2 mM soln. At the end of a 90 min application period, TMPA in the 1st turn, 1.4 mm from the base of ST, reached an av. concn. of 330 .mu.M (std. deviation (S.D.) 147

.mu.M, n = 8). TMPA in the second turn, 7.5 mm from the base of ST reached a concn. of 15 .mu.M (S.D. 33 .mu.M, n = 5). The measured time courses of TMPA concn. change were interpreted using the Washington University Cochlear Fluids Simulator (V 1.4), a public-domain program available on the internet. Simulations with parameters producing concn. time courses comparable to those measured were: (1) round window permeability: 1.9.times.10-8 cm/s; (2) ST clearance half-time: 60 min; (3) longitudinal perilymph flow rate: 4.4 nl/min, directed from base to apex. Solute concns. in apical regions of the cochlea were found to be detd. primarily by the rate at which the solute diffuses, balanced by the rate of clearance of the solute from perilymph. Longitudinal perilymph flow was not an important factor in solute distribution unless the bony otic capsule was perforated, which rapidly caused substantial changes to solute distribution. This study demonstrates the basic processes by which substances are distributed in the cochlea and provides a foundation to understand how other applied substances will be distributed in the ear.

SUPPL. TERM: mol uptake ear cochlea perilymph

INDEX TERM: Ear
(cochlea, perilymph; solute entry into cochlear perilymph through the round window membrane)

INDEX TERM: Biological transport
(uptake; solute entry into cochlear perilymph through the round window membrane)

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L19 ANSWER 5 OF 15 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:229790 HCAPLUS
DOCUMENT NUMBER: 135:142063
TITLE: Cochlear gene delivery through an intact **round window** membrane in mouse
AUTHOR(S): Jero, Jussi; Mhatre, Anand N.; Tseng, Charles J.; Stern, Ryan E.; Coling, Donald E.; Goldstein, Jayne A.; Hong, Keelung; Zheng, Wei Wen; Hoque, A. T. M. Shamsul; Lalwani, Anil K.
CORPORATE SOURCE: Laboratory of Molecular Otology, Epstein Laboratories, Department of Otolaryngology-Head and Neck Surgery, University of California San Francisco, San Francisco, CA, 94143, USA
SOURCE: Human Gene Therapy (2001), 12(5), 539-548
CODEN: HGTHE3; ISSN: 1043-0342
PUBLISHER: Mary Ann Liebert, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
CLASSIFICATION: 63-5 (Pharmaceuticals)
Section cross-reference(s): 1

ABSTRACT:
Cochlear gene transfer studies in animal models have utilized mainly two delivery methods: direct injection through the round window membrane (RWM) or intracochlear infusion through a cochleostomy. However, the surgical trauma, inflammation, and hearing loss assocd. with these methods lead us to investigate a less invasive delivery method. Herein, we studied the

feasibility of a vector transgene-soaked gelatin sponge, Gelfoam, for transgene
delivery into the mouse cochlea through an intact RWM. The Gelfoam absorbed
with liposomes and adenovirus, but not with adeno-assocd. virus (AAV), was successful in mediating transgene expression across an intact RWM in a variety
of cochlear tissues. The Gelfoam technique proved to be an easy, atraumatic,
and effective, but vector-dependent, method of delivering transgenes through an
intact RWM. Compared with the more invasive gene delivery methods, this technique represents a safer and a more clin. viable route of cochlear gene delivery in humans.

SUPPL. TERM: cochlea gene delivery membrane
INDEX TERM: Ear
(cochlea; cochlear gene delivery through an intact round
window membrane in mouse)
INDEX TERM: Adeno-associated virus
Drug delivery systems
Genetic vectors
Human adenovirus
Membranes, nonbiological
(cochlear gene delivery through an intact round window
membrane in mouse)
INDEX TERM: Transgene
ROLE: DEV (Device component use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cochlear gene delivery through an intact round window
membrane in mouse)
INDEX TERM: **Drug** delivery systems
(liposomes; cochlear gene delivery through an intact round window membrane in mouse)
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L19 ANSWER 6 OF 15 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:14959 HCAPLUS
DOCUMENT NUMBER: 132:44893
TITLE: Intratympanic therapy for Meniere's disease: high-concentration gentamicin with **round-window** protection
AUTHOR(S): Quaranta, A.; Aloisi, A.; De Benedittis, G.; Scaringi, A.
CORPORATE SOURCE: Department of Ophthalmology and Otorhinolaryngology, Audiology and Otology Pilot Center for Mediterranean Countries, University of Bari, Bari, 70124, Italy
SOURCE: Annals of the New York Academy of Sciences (1999), 884(Ototoxicity), 410-424
CODEN: ANYAA9; ISSN: 0077-8923
PUBLISHER: New York Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
CLASSIFICATION: 1-11 (Pharmacology)
ABSTRACT:
Many therapeutic options exist for the management of patients with Meniere's disease. In the last few years, the use of intratympanic gentamicin has been investigated as an alternative treatment to vestibular nerve section or labyrinthectomy. In humans, the concn. of gentamicin used for intratympanic treatment of vertigo ranges from 10 mg/mL to 40 mg/mL, and the no. of ***doses*** from 2 to 14, with a total administered amt. between 6 and 2,400 mg. Here lower **doses** of gentamicin were used, usually had the lowest incidence of hearing loss, but more injections were needed to ablate vestibular function. The purpose of this study was to evaluate the acute and chronic ototoxic effects of intratympanic high-concn. gentamicin after having obliterated the round-window niche with connective tissue in 11 subjects' ears with Meniere's disease. Intratympanic gentamicin was administered according to a predetd. and fixed schedule consisting of two **doses** of 0.5 mL

gentamicin soln., injected once a week with a **drug** concn. of 80 mg/mL. The total **dose** of gentamicin was .ltoreq. 80 mg. The charts of the patients were surveyed in accordance with the 1995 AAO-HNS guidelines.
Three patients had recurrence of vertigo between 3 and 6 mo after the second
injection and went on to one addnl. **dose** of gentamicin. At 2 yr follow-up, 10 patients (91%) had complete and 1 (9%) substantial control of vertigo; 3 subjects (27%) had hearing decreased. Tinnitus disappeared or decreased in 3 patients (27%); eight subjects (73%) reported their aural pressure abolished or decreased. The present study demonstrates that in patients with Meniere's disease, 0.5 mL gentamicin soln., with a concn. of 80
mg/mL (total **dose** .ltoreq. 80 mg), injected intratympanically once a week after having obliterated the round-window niche, permits complete or substantial control of vertigo in two-thirds of cases after two **doses** and in all subjects after three **doses**. This vertigo control rate is compared to that obsd. after vestibular nerve section. Hearing results are not
different from those with natural control, with endolymphatic sac surgery, and
with vestibular nerve section.

SUPPL. TERM: gentamicin tympanis Meniere disease vertigo
INDEX TERM: Ear
(Meniere's disease; high-**dose** gentamicin intratympanic therapy for Meniere's disease in humans)
INDEX TERM: Dizziness
Nervous system agents
(high-**dose** gentamicin intratympanic therapy for Meniere's disease in humans)
INDEX TERM: Ear
(tinnitus; high-**dose** gentamicin intratympanic therapy for Meniere's disease in humans)
INDEX TERM: Ear
(tympanic membrane; high-**dose** gentamicin intratympanic therapy for Meniere's disease in humans)
INDEX TERM: 1403-66-3, Gentamicin
ROLE: BAC (Biological activity or effector, except adverse);
BSU (Biological study, unclassified); THU (Therapeutic use);
BIOL (Biological study); USES (Uses)
(high-**dose** gentamicin intratympanic therapy for Meniere's disease in humans)
REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS

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L19 ANSWER 7 OF 15 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:750888 HCAPLUS
DOCUMENT NUMBER: 130:148265
TITLE: **Round window** administration of gentamicin: a new method for the study of ototoxicity of cochlear hair cells
AUTHOR(S): Husmann, Kathrin R.; Morgan, Adam S.; Girod, Douglas A.; Durham, Dianne
CORPORATE SOURCE: Department of Otolaryngology, the Smith Mental Retardation Research Center, University of Kansas Medical Center, Kansas City, KS, 66160-7380, USA
SOURCE: Hearing Research (1998), 125(1-2), 109-119
CODEN: HERED3; ISSN: 0378-5955
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
CLASSIFICATION: 1-5 (Pharmacology)
ABSTRACT:
Damage to inner ear sensory hair cells after systemic administration of ototoxic **drugs** has been documented in humans and animals. Birds have

the ability to regenerate new hair cells to replace those damaged by ***drugs*** or noise. Unfortunately, the systemic administration of gentamicin damages both ears in a variable fashion with potentially confounding systemic **drug** effects. The authors developed a method of direct application of gentamicin to one cochlea of hatchling chickens, allowing the other ear to serve as a within-animal control. The authors tested variables including the vehicle for application, location of application, **dosage**, and duration of gentamicin exposure. After 5- or 28-day survival, the percent length damage to the cochlea and regeneration of hair cells was evaluated using SEM. Controls consisted of the opposite unexposed cochlea and addnl. animals which received saline instead of gentamicin. Excellent damage was achieved using gentamicin-soaked Gelfoam pledgets applied to the round window membrane. The percent length damage could be varied from 15 to 100% by changing the **dosage** of gentamicin, with exposures as short as 30 min. No damage was obsd. in control animals. Regeneration of hair cells was obsd. in both the base and apex by 28-days survival.

SUPPL. TERM: gentamicin ototoxicity cochlear hair cell

INDEX TERM: Ear
(cochlea; round window administration of gentamicin: new method for study of ototoxicity of cochlear hair cells)

INDEX TERM: Ear
(organ of Corti, hair cell; round window administration of gentamicin: new method for study of ototoxicity of cochlear hair cells)

INDEX TERM: 1403-66-3, Gentamicin
ROLE: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(round window administration of gentamicin: new method for study of ototoxicity of cochlear hair cells)

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD.

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L19 ANSWER 8 OF 15 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:418137 HCAPLUS
DOCUMENT NUMBER: 129:197583
TITLE: Hair cell regeneration after local application of gentamicin at the **round window** of the cochlea in the pigeon
AUTHOR(S): Muller, Marcus; Smolders, Jean W. T.
CORPORATE SOURCE: Klinikum der J. W. Goethe-Universitat, Physiologisches Institut III, Frankfurt am Main, 60590, Germany
SOURCE: Hearing Research (1998), 120(1-2), 25-36
CODEN: HERED3; ISSN: 0378-5955
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
CLASSIFICATION: 1-5 (Pharmacology)
ABSTRACT:
Hair cells in the basilar papilla of birds have the capacity to regenerate after injury. Methods commonly used to induce cochlear damage are systemic application of ototoxic substances such as aminoglycoside **antibiotics** or loud sound. Both methods have disadvantages. The systemic application of ***antibiotics*** results in damage restricted to the basal 50% of the papilla and has severe side effects on the kidneys. Loud sound damages only

small parts of the papilla and is restricted to the short hair cells. The present study was undertaken to det. the effect of local aminoglycoside application on the physiol. and morphol. of the avian basilar papilla. Collagen sponges loaded with gentamicin were placed at the round window of the cochlea in adult pigeons. The time course of hearing thresholds was detd. from auditory brain stem responses elicited with pure tone bursts within a frequency range of 0.35-5.565 kHz. The condition of the basilar papilla was detd. from scanning electron micrographs. Five days after application of the collagen sponges loaded with gentamicin severe hearing loss, except for the lowest frequency tested, was obsd. Only at the apical 20% of the basilar papilla hair cells were left intact, all other hair cells were missing or damaged. At all frequencies there was little functional recovery until day 13 after implantation. At frequencies above 1 kHz functional recovery occurred at a rate of up to 4 dB/day until day 21, beyond that day recovery continued at a rate below 1 dB/day until day 48 at the 5.6 kHz. Below 1 kHz recovery occurred up to day 22, the recovery rate was below 2 dB/day. A residual hearing loss of about 15-25 dB remained at all frequencies, except for the lowest frequency tested. At day 20 new hair cells were seen on the basilar papilla. At day 48 the hair cells appeared to have recovered fully, except for the orientation of the hair cell bundles. The advantage of the local application of the aminoglycoside **drug** over systemic application is that it damages almost all hair cells in the basilar papilla and it has no toxic side effects. The damage is more extensive than with systemic application.

SUPPL. TERM: aminoglycoside gentamicin ototoxicity hair cell pigeon

INDEX TERM: **Antibiotics**
(aminoglycoside; hair cell regeneration after local application of gentamicin at the round window of the cochlea in the pigeon)

INDEX TERM: Ear
(cochlea; hair cell regeneration after local application of gentamicin at the round window of the cochlea in the pigeon)

INDEX TERM: Disease models

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Pigeon
(hair cell regeneration after local application of gentamicin at the round window of the cochlea in the pigeon)

INDEX TERM: Hearing
(loss; hair cell regeneration after local application of gentamicin at the round window of the cochlea in the pigeon)

INDEX TERM: Ear
(organ of Corti, hair cell; hair cell regeneration after local application of gentamicin at the round window of the cochlea in the pigeon)

INDEX TERM: Toxicity
(oto; hair cell regeneration after local application of gentamicin at the round window of the cochlea in the pigeon)

INDEX TERM: 1403-66-3, Gentamicin
ROLE: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hair cell regeneration after local application of gentamicin at the round window of the cochlea in the pigeon)

L19 ANSWER 9 OF 15 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:467438 HCAPLUS
DOCUMENT NUMBER: 122:235139
TITLE: Breakdown of the **round window** membrane permeability barrier evoked by streptolysin O: possible etiologic role in development of sensorineural hearing loss in acute otitis media
AUTHOR(S): Engel, Frank; Blatz, Rosemarie; Kellner, Jochen; Palmer, Michael; Weller, Ulrich; Bhakdi, Sucharit
CORPORATE SOURCE: Ear-Nose-Throat Clinic, Univ. Leipzig, Leipzig, Germany
SOURCE: Infect. Immun. (1995), 63(4), 1305-10
CODEN: INFIBR; ISSN: 0019-9567
DOCUMENT TYPE: Journal
LANGUAGE: English
CLASSIFICATION: 10-6 (Microbial, Algal, and Fungal Biochemistry)
ABSTRACT:
Sensorineural hearing loss is a common sequela of acute and chronic otitis media, and the round window membrane (RWM) is currently being considered as a

major route for noxious agents to pass from the middle ear cavity to the cochlea. Streptococcus pneumoniae, a major causative agent of otitis media,
and Streptococcus pyogenes A produce mol. related toxins, pneumolysin and streptolysin O (SLO), that form large pores in target membranes. In this study, we analyze the effects of SLO on the permeability of the RWM. Resected
RWMs from a total of 104 guinea pigs were embedded between two chambers of an
in vitro system. One chamber was designated as the tympanal (cis) compartment,
and the other was designated as the inner ear (trans) compartment. The permeability of normal and SLO-damaged RWMs towards Na+, [14C]mannitol, and proteins was investigated. SLO evoked permeability defects **dose** dependently in the RWM with fluxes of both Na+ and [14C]mannitol being demonstrable over a time span of up to 8 h. Serum proteins and radioiodinated
SLO were also shown to pass through the damaged RWM. SEM revealed the morphol.
correlates to these results. We propose that damage to the RWM by potent pore-forming cytolysins leads to leakage of ions from the perilymph. Ionic disequil. and passage of noxious macromols. to the cochlea could contribute to
disturbances of the inner ear function.

SUPPL. TERM: round window membrane permeability streptolysin O; ear round
window permeability streptolysin O

INDEX TERM: Hemolysins O
ROLE: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(effect of streptolysin O on the permeability of the round window membrane)

INDEX TERM: Ear
(disease, acute otitis media, effect of streptolysin O on
the permeability of the round window membrane in relation
to)

INDEX TERM: Biological transport
(permeation, effect of streptolysin O on the permeability
of the round window membrane)

INDEX TERM: Ear
(round window, effect of streptolysin O on the permeability of the round window membrane)

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09/205,251

L19 ANSWER 10 OF 15 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1994:692553 HCAPLUS
DOCUMENT NUMBER: 121:292553
TITLE: Average spectrum of spontaneous activity at the **round window** modified by sedation, anesthesia and salicylate
AUTHOR(S): Cazals, Y.; Huang, Z.
CORPORATE SOURCE: Hospital Pellegrin, Universite Bordeaux II, Bordeaux, 33076, Fr.
SOURCE: J. Phys. IV (1994), 4(C5, 3EME CONGRES FRANCAIS D'ACOUSTIQUE, 1994, VOL. 1), 415-18
CODEN: JPICEI; ISSN: 1155-4339
DOCUMENT TYPE: Journal
LANGUAGE: English
CLASSIFICATION: 1-11 (Pharmacology)
Section cross-reference(s): 2, 14

ABSTRACT:
The electrophysiol. signal recorded at the round window of the cochlea reflects sensory and neural activity of the inner ear. Besides acoustically evoked responses, sometimes temporally averaged, which are usual means of functional assessment; recordings obtained in silent conditions and spectrally averaged reflect spontaneous auditory nerve activity as recently demonstrated. In this paper it is shown that averaged spectrum of spontaneous activity (ASSA) at the round window of guinea pigs, with permanently implanted electrodes, differs in awake vs. sedated or anesthetized conditions. This casts some doubt upon the physiol. significance of single-unit analyses of spontaneous auditory nerve activity. It is also shown in this paper that ASSA is modified by administration of salicylate even at a **dose** which does not induce threshold elevation. These observations set ASSA at the round window as a convenient and very sensitive physiol. measure of spontaneous sensory-neural activity and provide much more convincing foundations for physiol. exploration of tinnitus in animal models.

SUPPL. TERM: salicylate ear round window sensory neuron; anesthesia ear round window sensory neuron; sedation ear round window sensory neuron
INDEX TERM: Anesthetics

(av. spectrum of spontaneous activity at round window modified by sedation, anesthesia and salicylate)
INDEX TERM: Ear
(inner, av. spectrum of spontaneous activity at round window modified by sedation, anesthesia and salicylate)
INDEX TERM: Mental activity
(sedation, av. spectrum of spontaneous activity at round window modified by sedation, anesthesia and salicylate)
INDEX TERM: 69-72-7, biological studies
ROLE: BAC (Biological activity or effector, except adverse);
BIOL (Biological study)
(av. spectrum of spontaneous activity at round window modified by sedation, anesthesia and salicylate)

L19 ANSWER 11 OF 15 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1991:240577 HCAPLUS
DOCUMENT NUMBER: 114:240577
TITLE: Effects of ear **drops** on the **round window** membrane, changes in permeability and thickness
AUTHOR(S): Ikeda, Katsuhisa; Morizono, Tetsuo; Takasaka, Tomonori
CORPORATE SOURCE: Sch. Med., Tohoku Univ., Sendai, 980, Japan
SOURCE: Ear Res. Jpn. (1990), 21(1), 253-4
CODEN: ERJAEA; ISSN: 0288-9781
DOCUMENT TYPE: Journal
LANGUAGE: English
CLASSIFICATION: 1-12 (Pharmacology)
Section cross-reference(s): 2

ABSTRACT:
The effects of ototopical prepns. (Cortisporin, Coly-Mycin, Aristocort, and Bestron) on the round window membrane (RWM) in chinchillas were studied by measuring the permeability to Et4N+ (K+-selective microelectrodes) and measuring the thickness (light microscopy). The RWM permeability was reduced
in Cortisporin- and Coly-Mycin-treated ears, and these 2 **drugs** caused a marked thickening of the RWM. In contrast, Aristocort and Bestron produced
no alteration of RWM permeability.

SUPPL. TERM: ear drop round window membrane; Cortisporin ear membrane;
Soly Mycin ear membrane; Aristocort ear membrane; Bestron

ear membrane
INDEX TERM: Ear
(round window, membrane, ear **drops** effect on)
INDEX TERM: 124-94-7, Aristocort 1066-17-7, Coly-Mycin
2667-89-2,
Beston 8024-64-4, Cortisporin
ROLE: BIOL (Biological study)
(ear round window membrane response to)

L19 ANSWER 12 OF 15 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1989:128596 HCAPLUS
DOCUMENT NUMBER: 110:128596
TITLE: The **round window** as access route for agents injurious to the inner ear
AUTHOR(S): Spandow, Odd; Anniko, Matti; Moeller, Aage R.
CORPORATE SOURCE: Dep. Oto-Rhino-Laryngol., Head Neck Surg. Otologic Res. Lab., Umea, Swed.
SOURCE: Am. J. Otolaryngol. (1988), 9(6), 327-35
CODEN: AJOTDP; ISSN: 0196-0709
DOCUMENT TYPE: Journal
LANGUAGE: English
CLASSIFICATION: 1-12 (Pharmacology)
Section cross-reference(s): 2

ABSTRACT:
The ototoxicity of 50% propylene glycol, 70% iso-Pr alc., 2% acetic acid, Otic Domeboro soln., 1% Gentian violet, Vosol Otic soln., Genoptic Ophthalmic soln., Cortisporin Otic suspension, Coly-Mycin S otic, and Pyocidin Otic was studied in rats by measuring their effect on the latencies of the second peak of the auditory brainstem responses (ABR) at different sound pressure levels. The substances were instilled into the round window (RW) niches of rats, and the ABR to 1-kHz and 6-kHz tonebursts were obtained, 30 min, 2 h, and 1 wk after exposure. For all substances except iso-Pr alc. and propylene glycol, which evidently quickly penetrated the RW, approx. 2 h of exposure were required before inner ear function was affected. The ototoxic effect of the ***antibiotic*** **drugs** was to some degree reversed with time, whereas the recorded potentials for antiseptics such as 1% Gentian violet, 2% acetic acid, and Otic Domeboro indicate that they caused severe damage in inner ear function. Some increases in latencies were also noted after exposure to

propylene glycol and iso-Pr alc., except when the latter was quickly withdrawn
from the RW mice.

SUPPL. TERM: **drug** toxicity ear evaluation; **antibiotic** toxicity ear evaluation; antiseptic toxicity ear evaluation
INDEX TERM: Toxicity
(of **drugs**, to inner ear, round window as access route for, evaluation of)
INDEX TERM: **Antibiotics**
Bactericides, Disinfectants, and Antiseptics
(toxicity of, to inner ear, round window as access route
for, evaluation of)
INDEX TERM: Ear
(inner, **drugs** toxicity to, evaluation of)
INDEX TERM: 57-55-6, Propylene glycol, biological studies 64-19-7, Acetic acid, biological studies 67-63-0, Isopropyl alcohol, biological studies 548-62-9, Gentian violet 8024-64-4, Cortisporin 99149-56-1, Otic Domeboro 119509-48-7, Coly-Mycin S Otic 119509-70-5, Genoptic Opthalmic 119510-02-0, Pyocidin Otic 119510-26-8, VoSol
ROLE: PRP (Properties)
(toxicity of, to inner ear, round window as access route
for, evaluation of)

L19 ANSWER 13 OF 15 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1984:465542 HCAPLUS
DOCUMENT NUMBER: 101:65542
TITLE: Permeability of the **round window** membrane
AUTHOR(S): Okuno, Taeko; Nomura, Yasuya
CORPORATE SOURCE: Fac. Med., Univ. Tokyo, Tokyo, Japan
SOURCE: Arch. Oto-Rhino-Laryngol. (1984), 240(2), 103-6
CODEN: AORLCG; ISSN: 0302-9530
DOCUMENT TYPE: Journal
LANGUAGE: English
CLASSIFICATION: 1-2 (Pharmacology)
ABSTRACT:
Cefmetazole [56796-20-4] passed through the round window membrane into the inner ear of the guinea pig. The concn. of the **drug** in the inner ear fluid indicated that a larger amt. of the **drug** reached the inner ear through the round window membrane than when administered i.p.

SUPPL. TERM: ear round window permeability cefmetazole

INDEX TERM: Ear
(round window, permeability of, to cefmetazole)
INDEX TERM: 56796-20-4
ROLE: BIOL (Biological study)
(ear round window permeability to)

L19 ANSWER 14 OF 15 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1980:87825 HCAPLUS
DOCUMENT NUMBER: 92:87825
TITLE: The penetration of gentamicin and neomycin into perilymph across the **round window** membrane
AUTHOR(S): Smith, Bruce M.; Myers, Martin G.
CORPORATE SOURCE: Univ. Iowa Hosp., Iowa City, IA, USA
SOURCE: Otolaryngol. Head Neck Surg. (1979), 87(6), 888-91
CODEN: OHNSDL; ISSN: 0194-5998
DOCUMENT TYPE: Journal
LANGUAGE: English
CLASSIFICATION: 1-2 (Pharmacodynamics)
ABSTRACT:
After exposure of the round window membrane of the auditory bulla of cats to
solns. contg. gentamicin sulfate [1405-41-0] or neomycin sulfate [1405-10-3]
at concns. similar to those commonly used in otic **drops**, the 2 aminoglycosides were recovered in the perilymph at concns. which had previously
been shown to cause histol. changes in the cochlea of guinea pigs. Thus, the
round window membrane is a permeable surface for potentially ototoxic levels of
aminoglycoside **antibiotics**.

SUPPL. TERM: aminoglycoside ear diffusion ototoxicity; gentamicin ear diffusion ototoxicity; neomycin ear diffusion ototoxicity
INDEX TERM: Ear
(inner, aminoglycosides diffusion from otic **drops** into, ototoxicity in relation to)
INDEX TERM: 1405-10-3 1405-41-0
ROLE: BIOL (Biological study)
(ear round window membrane permeability to, ototoxicity
in relation to)

L19 ANSWER 15 OF 15 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1966:450908 HCAPLUS
DOCUMENT NUMBER: 65:50908

09/205,251

ORIGINAL REFERENCE NO.: 65:9550h,9551a-b
TITLE: Acetylcholine suppression of the N1 component of **round window** recorded cochlear potentials
AUTHOR(S): Daigneault, E. A.; Brown, R. Don
CORPORATE SOURCE: Louisiana State Univ., New Orleans
SOURCE: Arch. Intern. Pharmacodyn. Therapie (1966), 162(1), 20-9
DOCUMENT TYPE: Journal
LANGUAGE: English
CLASSIFICATION: 68 (Pharmacodynamics)
ABSTRACT:
The effect of cholinergic **drugs** on the N1 component (indicates the state of conduction of the afferents) of round window membrane-recorded cochlear potentials was detd. in cats. Intraarterial (vertebral artery) administration of acetylcholine iodide (I) (5-10 .gamma./kg.) or methacholine chloride (II) (10-15 .gamma./kg.) produced significant N1 depression; intravenous administration of I was not an N1 depressant. Pretreatment of the cats with atropine sulfate (0.1 mg./kg. intraarterially) prevented N1 depression induced by I and II. Intraarterial administration of NaCl or nitroglycerin (0.1 mg./kg.) had no effect on the cochlear N1 component. Intraarterial administration of cetylethyldimethyl-ammonium bromide (III) (0.05-0.15 mg./kg.) 30 min. prior to I significantly enhanced the N1 depressant activity of I. III alone produced no significant N1 depression nor blood pressure change in the animals. Nitroglycerin produced no N1 depression and III significantly enhanced the N1 depression induced by I without a corresponding increase of its cardiovascular and respiratory effects, suggesting that local anoxia induced by the general cardiovacular effects of the cholinergics or by the local vasodilator activity on cochlear vessels was probably not the factor responsible for N1 depression. Acetylcholine probably plays a significant role in the inhibitory mechanism of the cochlea. 18 references.

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?ds

Set     Items   Description
S1     108398   (CONTROLL? OR DELAY? OR SUSTAIN?)(3N)(DELIVER? OR RELEASE?
              OR TARGET?)
S2       5048   ROUND()WINDOW?
S3          7   S1 AND S2
S4          2   MICRO()WICK?
S5          6   MICROWICK AND MEDICATION
S6          3   RD (unique items)
S7        587   AU='SILVERSTEIN H':AU='SILVERSTEIN HR'
S8         13   AU='SILVERSTEIN, H.':AU='SILVERSTEIN, H.H.'
S9        600   S7 OR S8
S10        28   S9 AND ROUND()WINDOW?
S11        11   RD (unique items)
S12        25   S10 NOT S6
S13         8   S11 NOT S6
S14  14730416   DRUG? OR MEDICATION? OR MEDICINE? OR ANTIBIOTIC? OR DOSAGE?
              OR DOSE? OR DROPS? OR MEDICINAL OR PHARMACEUTIC? OR REMEDY OR
              REMEDIES OR MEDICINAL? OR MEDICANT?
S15      1112   S14 AND S2
S16  11378820   S14/DE,TI
S17       734   S16 AND S2
S18       257   S17 AND S2/DE,TI
S19        82   S18 AND HUMAN
S20        80   S18 AND HUMAN/GS
S21        86   S18 AND HUMAN?
S22        86   S21 OR S20
S23        54   S22 AND PY<1999
S24        47   RD (unique items)
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?t s24/9/2,3

24/9/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10083245 99049711 PMID: 9833965
Round window **administration of gentamicin: a new method for the study of ototoxicity of cochlear hair cells.**
Husmann K R; Morgan A S; Girod D A; Durham D
Department of Otolaryngology and the Smith Mental Retardation Research Center, University of Kansas Medical Center, Kansas City 66160-7380, USA.
Hearing research (NETHERLANDS) Nov **1998** , 125 (1-2) p109-19, ISSN 0378-5955 Journal Code: 7900445
Contract/Grant No.: DC01589; DC; NIDCD
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Subfile: INDEX MEDICUS
Damage to inner ear sensory hair cells after systemic administration of ototoxic drugs has been documented in **humans** and animals. Birds have the ability to regenerate new hair cells to replace those damaged by drugs or noise. Unfortunately, the systemic administration of gentamicin damages both ears in a variable fashion with potentially confounding systemic drug effects. We developed a method of direct application of gentamicin to one cochlea of hatchling chickens, allowing the other ear to serve as a within-animal control. We tested variables including the vehicle for application, location of application, dosage, and duration of gentamicin exposure. After 5 or 28 days survival, the percent length damage to the cochlea and regeneration of hair cells was evaluated using scanning electron microscopy. Controls consisted of the opposite unexposed cochlea and additional animals which received saline instead of gentamicin. Excellent damage was achieved using gentamicin-soaked Gelfoam pledgets applied to the **round window** membrane. The percent length damage could be varied from 15 to 100% by changing the dosage of gentamicin, with exposures as short as 30 min. No damage was observed in control animals. Regeneration of hair cells was observed in both the base and apex by 28 days survival.
Tags: Animal; **Human** ; Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S
Descriptors: Gentamicins--administration and **dosage** --AD; *Gentamicins --toxicity--TO; *Hair Cells-- **drug** effects--DE; * **Round Window** -- **drug** effects--DE; Chickens; Gelatin Sponge, Absorbable; Hair Cells--injuries --IN; Hair Cells--physiology--PH; Microscopy, Electron, Scanning; Regeneration; Time Factors; Vehicles
CAS Registry No.: 0 (Gelatin Sponge, Absorbable); 0 (Gentamicins); 0 (Vehicles)
Record Date Created: 19990208

24/9/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10044115 99034135 PMID: 9818826
Hearing results of intratympanic steroid treatment of endolymphatic hydrops.
Arriaga M A; Goldman S
Division of Otolaryngology, Allegheny General Hospital, Pittsburgh, Pennsylvania 15212, USA.
Laryngoscope (UNITED STATES) Nov **1998** , 108 (11 Pt 1) p1682-5, ISSN 0023-852X Journal Code: 8607378
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Subfile: INDEX MEDICUS

OBJECTIVES/HYPOTHESIS: This study evaluated the effectiveness of a single application of steroids to the open middle ear in improving short-term hearing in patients with Meniere's disease and cochlear hydrops. STUDY DESIGN: Retrospective study in which each patient's pretreatment hearing served as the control compared with posttreatment hearing. METHODS: Patients were treated with a single application of dexamethasone, 8 mg, in hyaluronan. Following tympanotomy and lysis of **round window** adhesions, steroids were placed in the **round window** niche with absorbable gelatin sponge and the remainder of the middle ear was then filled with the steroid solution. Systemic steroids were not administered. Audiograms were performed within 1 month before surgery and at least 1 month after surgery. RESULTS: Between September 1996 and July 1997, 21 ears in 19 patients underwent intratympanic steroid treatment. The criterion for hearing change was a 10-dB or greater change in pure-tone average (PTA), or a 15% change in speech discrimination score (SDS). Of the 15 ears meeting inclusion criteria for this study, five (33%) demonstrated hearing improvement and three (20%) demonstrated hearing deterioration. Maximum improvement was a 38-dB improvement in PTA and a 32% improvement in SDS. CONCLUSION: A single application of intratympanic dexamethasone/hyaluronan solution directly to the **round window** did not produce dramatic short-term hearing improvement in patients with endolymphatic hydrops. Although the theoretical basis for intratympanic steroid treatment of endolymphatic hydrops is appealing, we urge close evaluation of the results of specific protocols of intratympanic steroid administration before widespread utilization of this treatment. The choice of steroid, route of administration, frequency of application, and need for simultaneous systemic administration require standardization to adequately assess the efficacy of this treatment.

Tags: Comparative Study; **Human**

Descriptors: Anti-Inflammatory Agents, Steroidal--therapeutic use--TU; *Dexamethasone--therapeutic use--TU; *Endolymphatic Hydrops-- **drug** therapy --DT; *Glucocorticoids, Topical--therapeutic use--TU; *Hearing--physiology --PH; *Meniere's Disease-- **drug** therapy--DT; Adhesions--surgery--SU; Adjuvants, Immunologic--administration and **dosage** --AD; Anti-Inflammatory Agents, Steroidal--administration and **dosage** --AD; Audiometry, Pure-Tone; Dexamethasone--administration and **dosage** --AD; Follow-Up Studies; Gelatin Sponge, Absorbable--administration and **dosage** --AD; Glucocorticoids, Topical--administration and **dosage** --AD; Hearing-- **drug** effects--DE; Hearing Disorders--etiology--ET; Hemostatics--administration and **dosage** --AD; Hyaluronic Acid--administration and **dosage** --AD; Retrospective Studies; **Round Window** --surgery--SU; Speech Perception-- **drug** effects --DE; Treatment Outcome; Tympanic Membrane--surgery--SU

CAS Registry No.: 0 (Adjuvants, Immunologic); 0 (Anti-Inflammatory Agents, Steroidal); 0 (Gelatin Sponge, Absorbable); 0 (Glucocorticoids, Topical); 0 (Hemostatics); 50-02-2 (Dexamethasone); 9004-61-9 (Hyaluronic Acid)

Record Date Created: 19981203

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?t s24/9/43,44

24/9/43 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

07879769 EMBASE No: 1999332322
Intratympanic and round - window drug **therapy: Effect on cochlear tinnitus**
Hicks G.W.
Dr. G.W. Hicks, Midwest Ear Institute, 7440 North Shadeland Avenue, Indianapolis, IN 46250 United States
AUTHOR EMAIL: ghicks@indy.net
International Tinnitus Journal (INT. TINNITUS J.) (United States) 1998, 4/2 (144-147)
CODEN: ITJOF ISSN: 0946-5448
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 16

Tinnitus is a common symptom for which few existing therapeutic approaches can produce reliable reduction or elimination. Chemical perfusion involves the delivery of medication directly into the inner ear via the **round - window** membrane. This report discusses the use of dexamethasone or gentamicin in 20 individuals who had inner ear diseases in which disturbing cochlear tinnitus was one of the symptoms. Preliminary results indicate that chemical perfusion is a promising option for the treatment of cochlear tinnitus.

BRAND NAME/MANUFACTURER NAME: xanax; pavabid; persantin; trental; tegretol; dilantin; prozac
DRUG DESCRIPTORS:
*dexamethasone--adverse **drug** reaction--ae; *dexamethasone-- **drug** therapy --dt; *gentamicin--adverse **drug** reaction--ae; *gentamicin-- **drug** therapy --dt
anxiolytic agent-- **drug** therapy--dt; vasodilator agent-- **drug** therapy--dt ; dipyridamole-- **drug** therapy--dt; nicotinic acid-- **drug** therapy--dt; pentoxifylline-- **drug** therapy--dt; local anesthetic agent-- **drug** therapy --dt; anticonvulsive agent-- **drug** therapy--dt; phenytoin-- **drug** therapy --dt; antihistaminic agent-- **drug** therapy--dt; antidepressant agent-- **drug** therapy--dt; amitriptyline-- **drug** therapy--dt; nortriptyline-- **drug** therapy--dt; fluoxetine-- **drug** therapy--dt; alprazolam; papaverine; carbamazepine
MEDICAL DESCRIPTORS:
*tinnitus-- **drug** therapy--dt; *tinnitus--therapy--th
reliability; **drug** delivery system; ototoxicity--side effect--si; disease classification; noise reduction; **human** ; male; female; clinical article; **human** tissue; **human** cell; aged; adult; article; priority journal
CAS REGISTRY NO.: 50-02-2 (dexamethasone); 1392-48-9, 1403-66-3, 1405-41-0 (gentamicin); 58-32-2 (dipyridamole); 54-86-4, 59-67-6 (nicotinic acid) ; 6493-05-6 (pentoxifylline); 57-41-0, 630-93-3 (phenytoin); 50-48-6, 549-18-8 (amitriptyline); 72-69-5, 894-71-3 (nortriptyline); 54910-89-3 , 56296-78-7, 59333-67-4 (fluoxetine); 28981-97-7 (alprazolam); 58-74-2 , 61-25-6 (papaverine); 298-46-4, 8047-84-5 (carbamazepine)
SECTION HEADINGS:
011 Otorhinolaryngology
027 Biophysics, Bioengineering and Medical Instrumentation
037 Drug Literature Index
038 Adverse Reaction Titles

24/9/44 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

07879768 EMBASE No: 1999332321

Round - Window **Microcatheter-administered microdose gentamicin: Results from treatment of tinnitus associated with Meniere's disease**

DeCicco M.J.; Hoffer M.E.; Kopke R.D.; Wester D.; Allen K.A.; Gottshall K.; O'Leary M.J.

M.E. Hoffer, Dept. of Defense Spatial Orientation, Department of Otolaryngology, Naval Medical Center, San Diego, CA 92134-5000 United States

AUTHOR EMAIL: mehoffer@nmcsd.med.navy.mil

International Tinnitus Journal (INT. TINNITUS J.) (United States) 1998, 4/2 (141-143)

CODEN: ITJOF ISSN: 0946-5448

DOCUMENT TYPE: Journal; Article

LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

NUMBER OF REFERENCES: 6

In this study, we review the results of Meniere's disease treatment using microdose gentamicin delivered directly to the **round window** using the **Round Window** Microcatheter (IntraEar, Inc., Denver, CO). A total of 18 patients were studied, with follow-up ranging from 6 to 18 months. In 15 of 18 patients (83%), tinnitus was improved significantly thruoghout the follow- up period. Vertigo was eliminated in all patients, and pressure was relieved in 17 of 18 (94%). These preliminary data suggest that **Round Window** Microcatheter-delivered gentamicin is a safe and effective treatment for the reduction of tinnitus, vertigo, and pressure associated with Meniere's disease.

DEVICE BRAND NAME/MANUFACTURER NAME: **Round Window** Microcatheter/ intraear/United States

DEVICE MANUFACTURER NAMES: intraear/United States

DRUG DESCRIPTORS:

*gentamicin--clinical trial--ct; *gentamicin-- **drug dose** --do; * gentamicin-- **drug** therapy--dt

MEDICAL DESCRIPTORS:

*tinnitus-- **drug** therapy--dt; *Meniere disease-- **drug** therapy--dt follow up; disease association; **drug** safety; **drug** efficacy; **drug** delivery system; catheterization; **dose** response; **human** ; clinical article; clinical trial; **human** tissue; **human** cell; article; priority journal

CAS REGISTRY NO.: 1392-48-9, 1403-66-3, 1405-41-0 (gentamicin)

SECTION HEADINGS:

008 Neurology and Neurosurgery

011 Otorhinolaryngology

027 Biophysics, Bioengineering and Medical Instrumentation

037 Drug Literature Index

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?t s24/9/8,9,10,17,18,23,30,45

24/9/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08771549 96148940 PMID: 8579132
Epinephrine-induced changes in human **cochlear blood flow.**
Miller J M; Laurikainen E A; Grenman R A; Suonpaa; Bredberg G
Kresge Hearing Research Institute, Department of Otolaryngology, University of Michigan, Ann Arbor 48109-0506, USA.
American journal of otology (UNITED STATES) May **1994** , 15 (3) p299-305; discussion 305-6, ISSN 0192-9763 Journal Code: 7909513
Contract/Grant No.: 5 R01 DC00105.; DC; NIDCD
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Subfile: INDEX MEDICUS
Cochlear blood flow (CBF) was monitored over the basal turn stria vascularis using laser Doppler flowmetry in five **human** subjects during middle ear surgery. The effects of systemically administered epinephrine (0.3 microgram/kg) and topically applied epinephrine (1:10,000) on the **round window** membrane (RWM) were examined. Topical epinephrine caused a mean reduction of 60 percent in CBF (maximum peak reduction 65-85% across subjects), which slowly recovered (> 10 min) toward baseline following epinephrine removal from the RWM. The changes in CBF are similar to those found in animal studies, but are much larger, indicating a relatively more pronounced role of adrenergic agents in CBF control in **humans** . Systemic epinephrine caused a 40 percent decrease in skin blood flow, a 90 percent increase in blood pressure (BP), above a resting hypotensive mean level of 65 mmHg, and a 50 percent increase in CBF. The CBF change followed the change in BP, but recovered toward baseline more slowly. The dramatic and somewhat prolonged decreases in CBF with RWM application of epinephrine may compromise sensory function and could account for the occasional unexplained sensorineural hearing loss or tinnitus associated with middle ear procedures that use topical epinephrine. The semipermeability of the RWM may, on the other hand, offer a route for therapeutic increases in CBF with vasodilative agents and provide an appropriate treatment for some cases of sensorineural hearing loss.
Tags: Comparative Study; Female; **Human** ; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S
Descriptors: Cochlea--blood supply--BS; *Cochlea-- **drug** effects--DE; *Epinephrine--pharmacology--PD; * **Round Window** -- **drug** effects--DE; Administration, Topical; Adolescence; Adult; Clinical Protocols; Epinephrine--administration and **dosage** --AD; Epinephrine--adverse effects --AE; Hearing Loss, Sensorineural--chemically induced--CI; Injections, Intravenous; Laser-Doppler Flowmetry; Time Factors; Tympanic Membrane --surgery--SU
CAS Registry No.: 51-43-4 (Epinephrine)
Record Date Created: 19960313

24/9/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08156516 94294155 PMID: 8022611
Streptomycin perfusion of the labyrinth through the round window **plus intravenous streptomycin.**
Shea J J; Ge X
Shea Clinic, Memphis, Tennessee.
Otolaryngologic clinics of North America (UNITED STATES) Apr **1994** , 27 (2) p317-24, ISSN 0030-6665 Journal Code: 0144042
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Subfile: INDEX MEDICUS
Streptomycin perfusion of the labyrinth through the **round window** membrane in the middle ear is a simple, safe, and effective way to stop the dizzy spells, fullness, and tinnitus of Meniere's disease without making the hearing worse. My results with 24 patients in the last 8 months are presented. Although the long-term effect of this operation remains to be seen, my experience with streptomycin perfusion of the labyrinth through the lateral semicircular canal leads me to believe these good results will be maintained in the future. Although the caloric response is not usually eliminated completely in the operated ear, it is reduced enough that the patient no longer has dizzy spells. Because the vestibular receptors are not completely destroyed, and the afferent and efferent nerves coming to and from them are undamaged, the patient compensates after this operation more quickly than when the vestibular receptors are completely destroyed by intramuscular or middle ear aminoglycoside, or when the afferent and efferent nerves of the vestibular receptors are cut as in labyrinthectomy or vestibular neurectomy. Hyaluronan is used to carry the streptomycin into the inner ear because it is known to penetrate the **round window** easily, and because being hygroscopic, it may reduce the amount of endolymph by osmosis.(ABSTRACT TRUNCATED AT 250 WORDS)
Tags: **Human**
Descriptors: Meniere's Disease--therapy--TH; *Streptomycin--administration and **dosage** --AD; Infusions, Intravenous; Injections; Labyrinth
CAS Registry No.: 57-92-1 (Streptomycin)
Record Date Created: 19940802

24/9/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08005451 94133850 PMID: 8302120
Sensorineural hearing loss from quinolinic acid: a neurotoxin in middle ear effusions.
Yellon R F; Rose E; Kenna M A; Doyle W J; Casselbrant M; Diven W F; Whiteside T L; Swarts J D; Heyes M P
Department of Pediatric Otolaryngology, Children's Hospital of Pittsburgh, PA 15213-2583.
Laryngoscope (UNITED STATES) Feb **1994** , 104 (2) p176-81, ISSN 0023-852X Journal Code: 8607378
Contract/Grant No.: DC00021; DC; NIDCD; DC01260; DC; NIDCD
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Subfile: INDEX MEDICUS
Quinolinic acid (QUIN) is an endogenous metabolite that exerts a neurotoxic effect by binding to specific neuronal receptors. Studies involving a broad spectrum of infectious and inflammatory central nervous system diseases have suggested a role for QUIN in causing neuronal injury. Since there is evidence for presence of the QUIN receptor in mammalian cochleas, QUIN was measured in middle ear effusions (MEEs). Gas chromatography/mass spectrometry detected QUIN in each of 65 diluted **human** MEEs, with a mean of 482 +/- 75 (SEM) nmol/L and a range from 15 to 2667 nmol/L. QUIN was also detected in each of 197 chinchilla MEEs from five different models of otitis media, with a mean of 10.6 +/- 1.3 (SEM) mumol/L and a range from 0.23 to 146.0 mumol/L (corrected for dilution). To determine whether QUIN causes sensorineural hearing loss (SNHL), QUIN solutions were placed on **round window** membranes (RWM) for 20 to 240 minutes, in 20 chinchillas. SNHL was detected by electrocochleography in QUIN-exposed animals, but not in saline controls. We conclude that QUIN is present in MEEs and that QUIN in the middle ear has the potential to cross the RWM and cause sensorineural hearing loss, possibly by binding to specific neuronal receptors in mammalian cochleas.
Tags: Animal; **Human** ; In Vitro; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S
Descriptors: Cochlea--innervation--IR; *Hearing Loss, Sensorineural

--chemically induced--CI; *Neurons-- **drug** effects--DE; *Otitis Media with Effusion--metabolism--ME; *Quinolinic Acid--adverse effects--AE; Audiometry, Evoked Response; Child; Chinchilla; Hearing Loss, Sensorineural --diagnosis--DI; Mass Fragmentography; Otitis Media with Effusion --complications--CO; Quinolinic Acid--analysis--AN; **Round Window -- drug** effects--DE
CAS Registry No.: 89-00-9 (Quinolinic Acid)
Record Date Created: 19940310

24/9/17 (Item 17 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

04581259 84253367 PMID: 6377855
Otological significance of the round window .
Nomura Y
Advances in oto-rhino-laryngology (SWITZERLAND) **1984** , 33 p1-162, ISSN 0065-3071 Journal Code: 0242534
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Subfile: INDEX MEDICUS
(336 Refs.)
Tags: Animal; Case Report; Female; **Human** ; Male; Support, Non-U.S. Gov't
Descriptors: Cochlea; *Ear Diseases--therapy--TH; * **Round Window** ; Adolescence; Adult; Aged; Ear Diseases--pathology--PA; Electrophysiology; Endolymphatic Sac--surgery--SU; Guinea Pigs; Hearing Disorders--chemically induced--CI; Hearing Disorders--etiology--ET; Labyrinthitis--pathology--PA ; Meniere's Disease--therapy--TH; Middle Age; Neomycin--adverse effects--AE ; Otitis Media with Effusion--physiopathology--PP; Otosclerosis--pathology --PA; Permeability; Pressure; **Round Window** --abnormalities--AB; **Round Window -- drug** effects--DE; **Round Window** --pathology--PA; **Round Window** --physiology--PH; **Round Window** --surgery--SU; **Round Window** --ultrastructure--UL; Rupture, Spontaneous; Virus Diseases--pathology--PA
CAS Registry No.: 1404-04-2 (Neomycin)
Record Date Created: 19840807

24/9/18 (Item 18 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

04046113 83033762 PMID: 7131638
The value of sodium chloride crystal application to the round window **for Meniere's disease.**
Longridge N S
Journal of otolaryngology (CANADA) Aug **1982** , 11 (4) p265-6, ISSN 0381-6605 Journal Code: 7610513
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Subfile: INDEX MEDICUS
Tags: Female; **Human** ; Male
Descriptors: Cochlea-- **drug** effects--DE; *Meniere's Disease-- **drug** therapy--DT; * **Round Window -- drug** effects--DE; *Sodium Chloride --administration and **dosage** --AD; Adult; Aged; Middle Age; Recurrence; Sodium Chloride--therapeutic use--TU
CAS Registry No.: 7647-14-5 (Sodium Chloride)
Record Date Created: 19821221

24/9/23 (Item 23 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

01519262 73024527 PMID: 5079597

Treatment of Meniere's disease by apposition of sodium chloride crystals on the round window .
Arslan M
Laryngoscope (UNITED STATES) Sep **1972** , 82 (9) p1736-50, ISSN 0023-852X Journal Code: 8607378
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Subfile: INDEX MEDICUS
Tags: Animal; **Human**
Descriptors: Meniere's Disease--therapy--TH; *Sodium Chloride --administration and **dosage** --AD; Cochlea; Guinea Pigs
CAS Registry No.: 7647-14-5 (Sodium Chloride)
Record Date Created: 19721229

24/9/30 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11320876 BIOSIS NO.: 199800102208
The role of dexamethasone or streptomycin perfusion in the treatment of Meniere's disease.
AUTHOR: Shea John J Jr(a)
AUTHOR ADDRESS: (a)Shea Clinic, 6133 Poplar Pike, Memphis, TN 38119**USA
JOURNAL: Otolaryngologic Clinics of North America 30 (6):p1051-1059 Dec., **1997**
ISSN: 0030-6665
DOCUMENT TYPE: Article
RECORD TYPE: Citation
LANGUAGE: English
REGISTRY NUMBERS: 50-02-2: DEXAMETHASONE; 57-92-1: STREPTOMYCIN
DESCRIPTORS:
MAJOR CONCEPTS: Otolaryngology (**Human** **Medicine** , Medical Sciences); Pharmacology
ORGANISMS: **human** --patient
ORGANISMS: PARTS ETC: endolymphatic sac--sensory system
DISEASES: endolymphatic hydrops--ear disease; vertigo--ear disease, nervous system disease; Meniere's disease--ear disease
CHEMICALS & BIOCHEMICALS: dexamethasone--antiinflammatory- **drug** , combination therapy, intravenous administration, oral administration, **round window** perfusion; streptomycin--combination therapy, perfusion, sclerosing agent
MISCELLANEOUS TERMS: blood-labyrinth barrier; dizzy spells; hearing
CONCEPT CODES:
20001 Sense Organs, Associated Structures and Functions-General; Methods
10060 Biochemical Studies-General
12512 Pathology, General and Miscellaneous-Therapy (1971-)
14501 Cardiovascular System-General; Methods
19001 Dental and Oral Biology-General; Methods
20501 Nervous System-General; Methods
22002 Pharmacology-General
BIOSYSTEMATIC CODES:
86215 Hominidae

24/9/45 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE

06801653 EMBASE No: 1997084138
Round window **membrane. Structure function and permeability: A review**
Goycoolea M.V.; Lundman L.
M.V. Goycoolea, San Crescente 70, Las Condes, Santiago Chile

Microscopy Research and Technique (MICROSC. RES. TECH.) (United States)
1997, 36/3 (201-211)
CODEN: MRTEE ISSN: 1059-910X
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 65

The ultrastructure of the **round window** membrane of **humans** , monkeys, felines, and rodents discloses three basic layers: an outer epithelium, a middle core of connective tissue, and an inner epithelium. Interspecies variations are mainly in terms of thickness, being thinnest in rodents and thicker in **humans** . Morphologic evidence suggests that the layers of the **round window** participate in absorption and secretion of substances to and from the inner ear, and that the entire membrane could play a role in the defense system of the ear. Different substances, including antibiotics, local anesthetics, and tracers such as cationic ferritin, horseradish peroxidase, and 1mu latex microspheres, are placed in the middle ear side traverse the membrane. Cationic ferritin and 1 micron microspheres placed in perilymph become incorporated by the inner epithelial cells of the membrane. Permeability is selective; factors include size, concentration, liposolubility, electrical charge, and thickness of the membrane. Passage of substances through the **round window** membrane is by different pathways, the nature of which is seemingly decided at the outer epithelium of the **round window** membrane.

DRUG DESCRIPTORS:
* **antibiotic** agent; *local anesthetic agent; *tracer
cation; ferritin; horseradish peroxidase; latex; microsphere
MEDICAL DESCRIPTORS:
*cochlea fenestra; *membrane permeability; *membrane structure
aging; cat; controlled study; epithelium cell; **human** ; monkey; nonhuman;
otitis media; priority journal; review; rodent; species difference
CAS REGISTRY NO.: 9007-73-2 (ferritin)
SECTION HEADINGS:
011 Otorhinolaryngology
029 Clinical and Experimental Biochemistry
?

3/9/1 (Item 1 from file: 144)
DIALOG(R)File 144:Pascal

15277815 PASCAL No.: 01-0448429

Round window **membrane delivery of L-methionine provides protection from cisplatin ototoxicity without compromising chemotherapeutic efficacy**

GEMING LI; FRENZ Dorothy A; BRAHMBLATT Sapna; FEGHALI Joseph G; RUBEN Robert J; BERGGREN Diana; AREZZO Joseph; VAN DE WATER Thomas R

Department of Otolaryngology, Albert Einstein College of Medicine, 1410 Pelham Parkway South, Kennedy Center, Room 302, Bronx NY, United States; Department of Anatomy and Structural Biology, Albert Einstein College of Medicine, Bronx NY, United States; Department of Otolaryngology, Beth Israel Medical Center, Albert Einstein College of Medicine, New York NY, United States; Department of Otolaryngology, University of Umea, Umea, Sweden; Department of Neuroscience, Albert Einstein College of Medicine, Bronx NY 10461, United States

Journal: Neurotoxicology : (Park Forest South), 2001, 22 (2) 163-176
ISSN: 0161-813X Availability: INIST-18397; 354000097196840010
No. of Refs.: 1 p.1/4
Document Type: P (Serial) ; A (Analytic)
Country of Publication: United States
Language: English

Cisplatin (cis-diamminedichloroplatinum(II) (CDDP)) is a widely used, highly effective, oncolytic agent that has serious ototoxic side-effects. To test the effectiveness of local delivery of L-methionine (L-Met) as an otoprotective agent against CDDP ototoxicity, we used a rat model of a highly metastatic breast cancer tumor, i.e. Fisher 344 rats implanted with MTLn3 breast cancer cells. Four experimental groups were evaluated - I: untreated; II: CDDP-treated (three dosages); III: systemically-delivered L-Met + CDDP-treated: IV: locally delivered L-Met + CDDP-treated. The integrity of the outer hair cells (OHCs) was determined using scanning electron microscopy (SEM); hearing was assessed by recording auditory brainstem responses (ABRs) at multiple frequencies. The chemotherapeutic effectiveness of CDDP was quantified by measuring changes in tumor mass and the presence of tumor metastasis. L-Met provided otoprotection of the OHCs against CDDP toxicity in the cochleae of rats following either systemic (III) or local (IV) administration. The ABRs were unchanged in each of the L-Met protection Groups (III and IV) and in the untreated animals of Group I. Treatment with CDDP only (II) induced significant hearing losses at both 16 and 18 kHz when compared to ABRs of untreated rats(I). CDDP was effective in controlling the MTLn3 initiated breast cancer tumors in the CDDP-treated (II) and the local L-Met protection, CDDP-treated (IV) Groups. In contrast, the tumors in the systemic L-Met protection, CDDP-treated Group (III) were not controlled by the CDDP treatment regime. This study demonstrates that local delivery of L-Met to the scala tympani of the cochlea via the **round window** membrane (IV) provides effective protection against CDDP ototoxicity without compromising its ability to control a highly metastatic form of cancer.

English Descriptors: Cisplatin; Alkylating agent; Antineoplastic agent; Methionine; Drug combination; Drug interaction; Toxicity; Organ of hearing; ENT; Metastasis; Malignant tumor; Breast disease; Animal; Rat; Strain specificity; Treatment; Chemotherapy; Prevention; Biological activity; Subcutaneous administration; **Controlled release** form; Platinum II Complexes; Intraperitoneal administration; Osmotic pump
Broad Descriptors: Rodentia; Mammalia; Vertebrata; ENT disease; Rodentia; Mammalia; Vertebrata; ORL pathologie; Rodentia; Mammalia; Vertebrata; ORL patologia

French Descriptors: Cisplatine; Agent alkylant; Anticancereux; Methionine; Association medicamenteuse; Interaction medicamenteuse; Toxicite; Appareil auditif; ORL; Metastase; Tumeur maligne; Sein pathologie; Animal ; Rat; Specificite souche; Traitement; Chimiotherapie; Prevention; Activite biologique; Voie souscutanee; Forme liberation controlee; Platine II Complexe; Voie intraperitoneale; Pompe osmotique

Classification Codes: 002B02U07

3/9/2 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13379023 BIOSIS NO.: 200200007844
Microdose gentamicin administration via the round window **microcatheter: Results in patients with Meniere's disease.**
BOOK TITLE: Annals of the New York Academy of Sciences The vestibular labyrinth in health and disease
AUTHOR: Hoffer Michael E(a); Kopke Richard D; Weisskopf Peter; Gottshall Kim; Allen Keith; Wester Derin
BOOK AUTHOR/EDITOR: Goebel Joel; Highstein Stephen M: Eds
AUTHOR ADDRESS: (a)CDR MC USN, Co-Director Department of Defense, Spatial Orientation Center, Department of Otolaryngology, Naval Medical Center San Diego, San Diego, CA, 92134-2200**USA E-Mail: mehoffer@nmcsd.med.navy.mil
JOURNAL: Annals of the New York Academy of Sciences (942):p46-51 October, 2001
MEDIUM: print
BOOK PUBLISHER: New York Academy of Sciences, 2 East 63rd Street, New York, NY, 10021, USA
CONFERENCE/MEETING: Vestibular Labyrinth in Health and Disease Conference Saint Louis, MO, USA November 16-18, 2000
ISSN: 0077-8923 ISBN: 1-57331-289-4 (cloth); 1-57331-290-8 (paper)
RECORD TYPE: Citation
LANGUAGE: English
REGISTRY NUMBERS: 1403-66-3: GENTAMICIN
DESCRIPTORS:
MAJOR CONCEPTS: Otolaryngology (Human Medicine, Medical Sciences); Pharmacology
BIOSYSTEMATIC NAMES: Hominidae--Primates; Mammalia, Vertebrata, Chordata, Animalia
ORGANISMS: human (Hominidae)--patient
BIOSYSTEMATIC CLASSIFICATION (SUPER TAXA): Animals; Chordates; Humans; Mammals; Primates; Vertebrates
DISEASES: Meniere's disease--drug therapy, ear disease
CHEMICALS & BIOCHEMICALS: gentamicin--microdose transtympanic administration, **sustained release**
METHODS & EQUIPMENT: **round window** microcatheter--drug delivery device
MISCELLANEOUS TERMS: Book Chapter; Meeting Paper
ALTERNATE INDEXING: Meniere's Disease (MeSH)
CONCEPT CODES:
00520 General Biology-Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals
10060 Biochemical Studies-General
12502 Pathology, General and Miscellaneous-General
12512 Pathology, General and Miscellaneous-Therapy (1971-)
20006 Sense Organs, Associated Structures and Functions-Pathology
22002 Pharmacology-General
22005 Pharmacology-Clinical Pharmacology (1972-)
BIOSYSTEMATIC CODES:
86215 Hominidae

3/9/3 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

11373259 EMBASE No: 2001386435
Microdose gentamicin administration via the Round Window

Microcatheter: Results in patients with Meniere's disease
Hoffer M.E.; Kopke R.D.; Weisskopf P.; Gottshall K.; Allen K.; Wester D.
M.E. Hoffer, Department of Defense, Spatial Orientation Center, Naval Medical Center San Diego, San Diego, CA 92134-2200 United States
AUTHOR EMAIL: mehoffer@nmcsd.med.navy.mil
Annals of the New York Academy of Sciences (ANN. NEW YORK ACAD. SCI.) (United States) 2001, 942/- (46-51)
CODEN: ANYAA ISSN: 0077-8923
DOCUMENT TYPE: Journal ; Conference Paper
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 15

Transtympanic gentamicin is becoming increasingly popular in the treatment of Meniere's disease. In this report we examine our experience with the use of microdose gentamicin via the **Round Window** Microcatheter for the treatment of Meniere's disease. Thirty-six patients were treated with gentamicin administration via the **Round Window** Microcatheter between July 1997 and August 2000. The patients all underwent 10 days of continuous treatment with a total dose of 2.4-3.75 mg of gentamicin (10 mg/ml). All patients had extensive pre-, intra-, and post-therapy auditory and vestibular testing. In this group, vertigo was eliminated in 89% of the patients, and tinnitus and pressure were significantly reduced in over 60% of the patients. Only one patient suffered a significant hearing loss and, most importantly, in all but one patient vestibular function was improved or normalized after treatment. **Round Window** Microcatheter-administered microdose gentamicin is an exciting new treatment for Meniere's disease. Preliminary results indicate that vertigo can be controlled without a significant reduction in cochlear or vestibular function in most patients. These results suggest that this therapy may be acting at a non-hair cell site. Our results are compared to the published literature examining transtympanic injection. In addition, the underlying science supporting this type of treatment is examined.

DRUG DESCRIPTORS:
*gentamicin--adverse drug reaction--ae; *gentamicin--drug administration --ad; *gentamicin--drug dose--do; *gentamicin--drug therapy--dt; * gentamicin--topical drug administration--tp
MEDICAL DESCRIPTORS:
*Meniere disease
cochlea fenestra; catheterization; vertigo--drug therapy--dt; vertigo --prevention--pc; tinnitus--drug therapy--dt; tinnitus--prevention--pc; hearing loss--side effect--si; hair cell; **sustained release** preparation ; human; male; female; clinical article; aged; adult; conference paper
CAS REGISTRY NO.: 1392-48-9, 1403-66-3, 1405-41-0 (gentamicin)
SECTION HEADINGS:
011 Otorhinolaryngology
037 Drug Literature Index
038 Adverse Reaction Titles

3/9/4 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

10773875 EMBASE No: 2000254076
Round window **membrane permeability to transforming growth factor-alpha: An in vitro study**
Witte M.C.; Kasperbauer J.L.
Dr. J.L. Kasperbauer, Mayo Clinic, 200 First Street SW, Rochester, MN 55905 United States
Otolaryngology - Head and Neck Surgery (OTOLARYNGOL. HEAD NECK SURG.) (United States) 2000, 123/1 I (91-96)
CODEN: OTOLD ISSN: 0194-5998
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 17

OBJECTIVE: Recent studies have identified the capacity of transforming growth factor-alpha (TGF-alpha) to stimulate mammalian labyrinthine hair cell regeneration after acute ototoxic damage. Augmenting hair cell regeneration with such growth factors may have a role in potentiation of recovery of cochlear function after hair cell injury. Transtympanic application of aqueous solutions to the **round window** membrane (RWM) has proved successful as a drug delivery route. The purpose of this study was to test the permeability of the mammalian RWM to TGF-alpha in an inexpensive and reliable in vitro model. METHODS: Guinea pig RWM niches were harvested and transferred to a 2-chamber apparatus, and TGF-alpha was applied to the middle-ear side of the chamber. ELISAs of TGF-alpha were measured at intervals during a 96-hour period. RESULTS: Aliquots taken during a 96-hour interval demonstrated passage of TGF-alpha in concentrations sufficient to stimulate hair cell regrowth. CONCLUSIONS: The apparatus allows study of RWM permeability to other substances and provides a basic model for study of RWM physiology. TGF-alpha is able to pass through a mammalian RWM.

MANUFACTURER NAMES: Calbiochem
DRUG DESCRIPTORS:
*transforming growth factor alpha--pharmaceutics--pr; *transforming growth factor alpha--pharmacokinetics--pk; *transforming growth factor alpha --pharmacology--pd
MEDICAL DESCRIPTORS:
*membrane permeability; *cochlea fenestra; *drug transport
guinea pig; hair cell; cell growth; concentration response; drug **delivery** system; nonhuman; male; **controlled** study; animal tissue; article
SECTION HEADINGS:
011 Otorhinolaryngology
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
039 Pharmacy

3/9/5 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

10238632 Genuine Article#: BT31Q Number of References: 15
Title: Microdose gentamicin administration via the round window **microcatheter - Results in patients with Meniere's disease**
Author(s): Hoffer ME (REPRINT) ; Kopke RD; Weisskopf P; Gottshall K; Allen K; Wester D
Corporate Source: Naval Med Ctr San Diego,Dept Def, Spatial Orientat Ctr, Dept Otolaryngol,San Diego//CA/92134 (REPRINT); Naval Med Ctr San Diego,Dept Def, Spatial Orientat Ctr, Dept Otolaryngol,San Diego//CA/92134
, 2001, V942, P46-51
ISSN: 0077-8923 Publication date: 20010000
Publisher: NEW YORK ACAD SCIENCES, 2 EAST 63RD ST, NEW YORK, NY 10021 USAVESTIBULAR LABYRINTH IN HEALTH AND DISEASE
Series: ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
Language: English Document Type: ARTICLE
Geographic Location: USA
Journal Subject Category: MULTIDISCIPLINARY SCIENCES
Abstract: Transtympanic gentamicin is becoming increasingly popular in the treatment of Meniere's disease. In this report we examine our experience with the use of microdose gentamicin via the **Round Window** Microcatheter for the treatment of Meniere's disease. Thirty-six patients were treated with gentamicin administration via the **Round Window** Microcatheter between July 1997 and August 2000. The patients all underwent 10 days of continuous treatment with a total dose of 2.4-3.75 mg of gentamicin (10 mg/ml). All patients had extensive pre-, intra-, and post-therapy auditory and vestibular testing. In this group, vertigo was eliminated in 89% of the patients, and tinnitus and

pressure were significantly reduced in over 60% of the patients. Only one patient suffered a significant hearing loss and, most importantly, in all but one patient vestibular function was improved or normalized after treatment. **Round Window** Microcatheter-ad ministered microdose gentamicin is an exciting new treatment for Meniere's disease. Preliminary results indicate that vertigo can be controlled without a significant reduction in cochlear or vestibular function in most patients. These results suggest that this therapy may be acting at a non-hair cell site. Our results are compared to the published literature examining transtympanic injection. In addition, the underlying science supporting this type of treatment is examined.
Descriptors--Author Keywords: meniere's disease ; gentamicin ; **sustained release** ; vertigo
Identifiers--KeyWord Plus(R): INTRATYMPANIC GENTAMICIN; THERAPY
Cited References:
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NEDZELSKI JM, 1993, V14, P278, AM J OTOL
ODKVIST LM, 1989, V457, P83, ACTA OTOLARYNGOL S S
PARNES LS, 1993, V103, P745, LARYNGOSCOPE
PENDER DJ, 1985, V6, P358, AM J OTOLARYNG
PYYKKO I, 1994, V110, P162, OTOLARYNG HEAD NECK
RAUCH SD, 1997, V107, P49, LARYNGOSCOPE

3/9/6 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

10163515 Genuine Article#: 491WE Number of References: 15
Title: Use of the round window **microcatheter in the treatment of Meniere's disease**
Author(s): Hoffer ME (REPRINT) ; Kopke RD; Weisskopf P; Gottshall K; Allen K; Wester D; Balaban C
Corporate Source: USN,Med Ctr San Diego, Dept Otolaryngol, Dept Def Spatial Orientat Ctr,San Diego//CA/92134 (REPRINT); USN,Med Ctr San Diego, Dept Otolaryngol, Dept Def Spatial Orientat Ctr,San Diego//CA/92134
Journal: LARYNGOSCOPE, 2001, V111, N11,1 (NOV), P2046-2049
ISSN: 0023-852X Publication date: 20011100
Publisher: LIPPINCOTT WILLIAMS & WILKINS, 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA
Language: English Document Type: ARTICLE
Geographic Location: USA
Journal Subject Category: MEDICINE, RESEARCH & EXPERIMENTAL; OTORHINOLARYNGOLOGY
Abstract: Objectives/Hypothesis: Transtympanic gentamicin is an increasingly popular treatment for Meniere's disease. The present report examines the 2-year follow-up of our first 27 patients with Meniere's disease treated with the use of microdose gentamicin through the **Round Window** Microcatheter. We applied the 1995 American Academy of Otolaryngology-Head and Neck Surgery criteria to this patient group to analyze the results of treatment. Study Design: This study is an evaluation of consecutive patients with predetermined data collection on each patient. Methods: Patients with confirmed Meniere's disease underwent placement of the **Round Window** Microcatheter, which was filled with 10 mg/mL gentamicin, after placement into the **round window** niche was confirmed. Ten milligrams per milliliter of gentamicin was injected into the catheter by hand on two occasions after device placement in the first several patients. The remaining

patients had continuous infusion of 10 mg/mL gentamicin at 1 muL/h for the next 10 days. The catheter was removed 10 days after placement. All patients underwent an extensive set of hearing and vestibular tests on several occasions before, during, and after treatment. Results: In the patients in the study, vertigo was eliminated in 92.6%, with 3.7% of patients (1/27) demonstrating a mild permanent threshold shift in hearing. Tinnitus and pressure were significantly reduced in more than 65% of patients. Only one patient demonstrated a reduction of vestibular function after treatment. Conclusions: Results of this study on this group of patients indicate that vertigo can be controlled in the long term using microdose gentamicin without a significant reduction in cochlear or vestibular function in most of the patients in our series. Our results are compared with the published literature examining transtympanic injection. In addition, the underlying science supporting this type of treatment is examined.

Descriptors--Author Keywords: gentamicin ; Meniere's disease ; **sustained - release** device ; vertigo ; hearing loss

Identifiers--KeyWord Plus(R): INTRATYMPANIC GENTAMICIN; THERAPY

Cited References:

CORSTEN M, 1997, V26, P361, J OTOLARYNGOL
DECICCO MJ, 1998, V4, P141, INT TINNITUS J
DRISCOLL CLW, 1997, V107, P83, LARYNGOSCOPE
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NEDZELSKI JM, 1993, V14, P278, AM J OTOL
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PARNES LS, 1993, V103, P745, LARYNGOSCOPE
PENDER DJ, 1985, V6, P358, AM J OTOLARYNG
PYYKKO I, 1994, V110, P162, OTOLARYNG HEAD NECK
RAUCH SD, 1997, V107, P49, LARYNGOSCOPE

3/9/7 (Item 3 from file: 34)

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

09538321 Genuine Article#: 416FX Number of References: 21

Title: Quantification of solute entry into cochlear perilymph through the round window membrane

Author(s): Salt AN (REPRINT) ; Ma YL

Corporate Source: Washington Univ,Sch Med, Dept Otolaryngol,Box 8115,660 S Euclid Ave/St Louis//MO/63110 (REPRINT); Washington Univ,Sch Med, Dept Otolaryngol,St Louis//MO/63110

Journal: HEARING RESEARCH, 2001, V154, N1-2 (APR), P88-97

ISSN: 0378-5955 Publication date: 20010400

Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS

Language: English Document Type: ARTICLE

Geographic Location: USA

Journal Subject Category: NEUROSCIENCES; OTORHINOLARYNGOLOGY

Abstract: The administration of drugs to the inner ear via the **round window** membrane is becoming more widely used for both clinical and experimental purposes. The actual drug levels achieved in different regions of the inner ear by this method have not been established. The present study has made use of simulations of solute movements in the cochlear fluids to describe the distribution of a marker solute in the guinea pig cochlear fluid spaces. Simulation parameters were derived from experimental measurements using a marker ion. trimethylphenylammonium (TMPA). The distribution of this ion in the cochlea was monitored without volume disturbance using TMPA-selective microelectrodes sealed into the first and second turns of scala tympani (ST). TMPA was applied to perilymph by irrigation of the intact **round window** membrane with 2 mM solution. At the end of a 90 min

application period, TMPA in the first turn, 1.4 mm from the base of ST, reached an average concentration of 330 muM (standard deviation (S.D.) 147 muM, n = 8). TMPA in the second turn. 7.5 mm from the base of ST reached a concentration of 15 muM (S.D. 33 muM, n = 5). The measured time courses of TMPA concentration change were interpreted using the Washington University Cochlear Fluids Simulator (V 1.4), a public-domain program available on the internet at http://oto.wustl.edu/cochlea/. Simulations with parameters producing concentration time courses comparable to those measured were: (1) **round window** permeability: 1.9X10(-8) cm/s; (2) ST clearance half-time: 60 min: (3) longitudinal perilymph flow rate: 4.4 nl/min, directed from base to apex. Solute concentrations in apical regions of the cochlea were found to be determined primarily by the rate at which the solute diffuses, balanced by the rate of clearance of the solute from perilymph. Longitudinal perilymph now was not an important factor in solute distribution unless the bony otic capsule was perforated. which rapidly caused substantial changes to solute distribution. This study demonstrates the basic processes by which substances are distributed in the cochlea and provides a foundation to understand how other applied substances will be distributed in the ear.

Descriptors--Author Keywords: cochlea ; perilymph ; **round window** membrane

Identifiers--KeyWord Plus(R): **SUSTAINED - RELEASE** VEHICLE; GUINEA-PIG COCHLEA; INNER-EAR; RADIAL COMMUNICATION; GENTAMICIN; INJECTION; SCALAE; TRACER; SPACE; FLOW

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SALT AN, 1995, V88, P79, HEARING RES
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SILVERSTEIN H, 1999, V78, P595, EAR NOSE THROAT J
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?t s6/9/1-3

6/9/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11316374 21373650 PMID: 11480300
Use of the malleus handle as a landmark for localizing the round window membrane.
Silverstein H; Durand B; Jackson L E; Conlon W S; Rosenberg S I
Ear Research Foundation, 1901 Floyd St., Sarasota, FL 34239, USA. hsilverste@aol.com
Ear, nose, & throat journal (United States) Jul 2001, 80 (7) p444-5, 448, ISSN 0145-5613 Journal Code: 7701817
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Subfile: INDEX MEDICUS
Localization of the round window membrane is desirable in order to allow a more direct application of **medication** to the inner ear. A new procedure has been developed to deliver direct, near-continuous inner ear perfusion to the round window with the Silverstein **MicroWick** . In this office procedure, the wick is inserted through a tympanostomy tube into the round window niche. Accurate localization of the round window is a necessary component of this procedure. In an effort to ascertain the precise location of the round window, we examined 25 cadaveric human temporal bones and measured the distance from the umbo to the round window in each sample. We found that the round window was an average of 3.44 mm (+/- 0.68) from the umbo and was situated at an average angle of 113.2 degrees (+/- 9.8) from the long process of the malleus. Our simple and reliable determination of the relationship between the malleus handle and the round window niche allows for the accurate placement of the Silverstein **MicroWick** and other devices.
Tags: Human; Support, Non-U.S. Gov't
Descriptors: *Drug Delivery Systems--methods--MT; *Malleus--anatomy and histology--AH; *Round Window--anatomy and histology--AH; *Temporal Bone --anatomy and histology--AH; Cadaver; Drug Delivery Systems --instrumentation--IS; Meniere's Disease--drug therapy--DT; Middle Ear Ventilation
Record Date Created: 20010801

6/9/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10426691 99414810 PMID: 10485154
Use of a new device, the MicroWick , **to deliver** medication **to the inner ear.**
Silverstein H
Ear Research Foundation, Sarasota, Fla. 34239, USA. earsinus@aol.com
Ear, nose, & throat journal (UNITED STATES) Aug 1999, 78 (8) p595-8, 600, ISSN 0145-5613 Journal Code: 7701817
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Subfile: INDEX MEDICUS
A new procedure for delivering **medication** directly to the inner ear has been developed. This delivery system, called the **MicroWick** , involves the use of a small wick that is inserted through a tympanic membrane vent tube into the round window niche. Once the wick has been inserted, the patient can self-administer eardrops into the ear canal, where they are absorbed by the wick and transported to the round window membrane and to the inner ear fluids. Inserting the wick is a minor procedure that is performed in the office. This paper describes the indications for and use of the **MicroWick** . (14 Refs.)

Tags: Human
Descriptors: *Drug Delivery Systems--instrumentation--IS; *Ear Diseases --drug therapy--DT; Antibiotics--administration and dosage--AD; Autoimmune Diseases--drug therapy--DT; Deafness, Sudden--drug therapy--DT; Dexamethasone--administration and dosage--AD; Equipment Design; Gentamicins --administration and dosage--AD; Labyrinth--physiopathology--PP; Labyrinth --surgery--SU; Meniere's Disease--drug therapy--DT; Sensitivity and Specificity; Steroids--administration and dosage--AD; Surgical Procedures, Minimally Invasive
CAS Registry No.: 0 (Antibiotics); 0 (Gentamicins); 0 (Steroids); 50-02-2 (Dexamethasone)
Record Date Created: 19991008

6/9/3 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

07811789 EMBASE No: 1999301353
Use of a new device, the MicroWick **(TM), to deliver** medication **to the inner ear**
Silverstein H.
Dr. H. Silverstein, Ear Research Foundation, 1901 Floyd St., Sarasota, FL 34239 United States
AUTHOR EMAIL: earsinus@aol.com
Ear, Nose and Throat Journal (EAR NOSE THROAT J.) (United States) 1999, 78/8 (595-600)
CODEN: ENTJD ISSN: 0145-5613
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 14

A new procedure for delivering **medication** directly to the inner ear has been developed. This delivery system, called the **MicroWick** (TM), involves the use of a small wick that is inserted through a tympanic membrane vent tube into the round window niche. Once the wick has been inserted, the patient can self-administer eardrops into the ear canal, where they are absorbed by the wick and transported to the round window membrane and to the inner ear fluids. Inserting the wick is a minor procedure that is performed in the office. This paper describes the indications for and use of the **MicroWick** .

DEVICE BRAND NAME/MANUFACTURER NAME: **MicroWick**
DRUG DESCRIPTORS:
*ear drops
dexamethasone; steroid
MEDICAL DESCRIPTORS:
*drug delivery system; *inner ear
eardrum; cochlea fenestra; treatment indication; safety; functional anatomy ; human; topical drug administration; article
CAS REGISTRY NO.: 50-02-2 (dexamethasone)
SECTION HEADINGS:
011 Otorhinolaryngology
027 Biophysics, Bioengineering and Medical Instrumentation
037 Drug Literature Index
?

13/9/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10253883 99246433 PMID: 10229588
Direct round window membrane application of gentamicin in the treatment of Meniere's disease.
Silverstein H ; Arruda J; Rosenberg S I; Deems D; Hester T O
Ear Research Foundation, Sarasota, FL 34239, USA.
Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery (UNITED STATES) May 1999, 120 (5) p649-55, ISSN 0194-5998 Journal Code: 8508176
Document type: Clinical Trial; Controlled Clinical Trial; Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Subfile: INDEX MEDICUS
OBJECTIVE: To evaluate the effectiveness of the **round window** membrane (RWM) Gelfoam gentamicin technique in patients with Meniere's disease who were unresponsive to medical management or in whom surgical therapy failed.Study Design: Protocol 1, single intratympanic gentamicin infusion; protocol 2 (the best method), 2 infusions, 5 days apart with reevaluation at 1 month; and protocol 3, multiple infusions 1 to 4 weeks apart. PATIENTS: In total, 32 patients (19 male, 13 female) were enrolled in the study. The mean age was 65 years (range 34 to 94 years). Seven of these patients were surgical salvage cases. INTERVENTIONS: Laser-assisted otoendoscopy with a 1.7-mm otoendoscope (Smith-Nephew Richards, Memphis, TN) was performed first. If the RWM was obscured by mucosa or adhesions, these were cleared before placing a 2 x 3 mm piece of dry Gelfoam against the RWM. Buffered gentamicin (26.7 mg/mL) was then injected into the middle ear (0.2 to 0.3 mL). RESULTS: Overall, vertigo was controlled in 75% of the patients after the completion of the treatment, with subtotal vestibular ablation in two thirds of patients. Hearing was preserved in 90% of the patients (within 15 dB pure-tone average or 15% speech discrimination score), tinnitus improved in 48%, and aural pressure improved in 62.5%.
Tags: Female; Human; Male; Support, Non-U.S. Gov't
Descriptors: Antibiotics, Aminoglycoside--administration and dosage--AD; *Gelatin Sponge, Absorbable--administration and dosage--AD; *Gentamicins --administration and dosage--AD; *Meniere's Disease--drug therapy--DT; * **Round Window** ; Adult; Aged; Aged, 80 and over; Audiometry; Caloric Tests ; Clinical Protocols; Drug Administration Schedule; Endoscopy; Injections; Instillation, Drug; Laser Surgery; Meniere's Disease--complications--CO; Meniere's Disease--diagnosis--DI; Middle Age; Middle Ear Ventilation; Time Factors; Treatment Outcome
CAS Registry No.: 0 (Antibiotics, Aminoglycoside); 0 (Gelatin Sponge, Absorbable); 0 (Gentamicins)
Record Date Created: 19990601

13/9/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09048378 96425961 PMID: 8828271
Intratympanic steroid treatment of inner ear disease and tinnitus (preliminary report).
Silverstein H ; Choo D; Rosenberg S I; Kuhn J; Seidman M; Stein I
Ear Research Foundation, Sarasota, FL 34239, USA.
Ear, nose, & throat journal (UNITED STATES) Aug 1996, 75 (8) p468-71, 474, 476 passim, ISSN 0145-5613 Journal Code: 7701817
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Subfile: INDEX MEDICUS
Intratympanic instillation of Depo-Medrol (80 mg/cc), dexamethasone ophthalmic solution (1 mg/cc), or dexamethasone intravenous (4 mg/cc) solution produces improvement of cochlear function in certain patients with

Meniere's disease, autoimmune inner ear disease and sudden sensorineural deafness. Tinnitus improved in 47%, most often in patients with Meniere's disease (9 of 15; 60%). The SRT improvement of greater than 10 dB or SD greater than 15% was documented in 41% (average improvement in SRT: 15 dB; SD: 24%). Patients with tinnitus and bilateral sensorineural hearing loss (i.e., presbycusis) did not benefit from the treatment. Prior to treatment with intratympanic medication, laser assisted tympanostomy with middle ear exploration, using otoendoscopy to determine the status of the **round window** niche and remove mucosal folds, helps in making the **round window** membrane accessible to local application of drops. Placing Gelfoam into the **round window** niche under direct vision, and using a Venturi Bobbin tube in the tympanic membrane, appears to be a satisfactory method for delivering medication to the inner ear fluids. The medication can be injected by the physician through the tube into the middle ear, or the patient can perform self-treatment at home, placing medication in the external auditory canal. A double-blind, cross-over study in patients with Meniere's disease is now in progress with Institutional Review Board (IRB) approval, which will be reported at a later date. This preliminary study has shown that intratympanic steroids may affect the symptoms of hearing loss and tinnitus in patients with various inner ear problems. Patients with Meniere's disease appear to respond in the highest percentage of cases. Hopefully, additional research will suggest the appropriate drugs which can be used to treat inner ear disease. Direct application of the drug to the **round window** membrane may increase the concentration in the inner ear fluids, thus avoiding the systemic effects.

Tags: Animal; Case Report; Comparative Study; Human; Male; Support, Non-U.S. Gov't

Descriptors: *Anti-Inflammatory Agents, Steroidal--pharmacology--PD; *Dexamethasone--pharmacology--PD; *Meniere's Disease--complications--CO; *Tinnitus--complications--CO; *Tinnitus--drug therapy--DT; *Tympanic Membrane--drug effects--DE; *Tympanic Membrane--physiopathology--PP; Aged; Anti-Inflammatory Agents, Steroidal--therapeutic use--TU; Dexamethasone --therapeutic use--TU; Guinea Pigs; Labyrinth--drug effects--DE; Labyrinth --physiopathology--PP; Meniere's Disease--physiopathology--PP

CAS Registry No.: 0 (Anti-Inflammatory Agents, Steroidal); 50-02-2 (Dexamethasone)

Record Date Created: 19961125

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Set     Items   Description
S1        243   ROUND()WINDOW? OR RWM
S2       4503   (CONTROL? OR DELAY? OR SUSTAIN?)(3N)(DELIVER? OR RELEASE? -
            OR TARGET?)
S3     204021   DRUG? OR MEDICATION? OR MEDICINE? OR ANTIBIOTIC? OR DOSAGE?
            OR DOSE? OR DROPS? OR MEDICINAL? OR PHARMACEUTIC? OR REMEDY -
            OR REMEDIES OR MEDICINAL? OR MEDICANT?
S4         20   S1 (5N)2
S5         20   RD (unique items)
S6        156   S1 AND S3
S7          2   S1 AND S2 AND S3
S8        101   S6 AND HUMAN?
S9         82   S8 AND PY<1999
S10        82   RD (unique items)
S11         6   S10 AND S1/DE,TI
S12         5   S1(3N)S3
?show files
File 457:The Lancet 1986-2000/Oct W1
         (c) 2000 The Lancet, Ltd.
File 444:New England Journal of Med. 1985-2002/May W3
         (c) 2002 Mass. Med. Soc.
File 442:AMA  Journals 1982-2002/May B2
         (c)2002 Amer Med Assn -FARS/DARS apply
File 441:ESPICOM Pharm&Med DEVICE NEWS 2002/May W3
         (c) 2002 ESPICOM Bus.Intell.
File 198:Health Devices Alerts(R) 1977-2002/May W3
         (c) 2002 ECRI-nonprft agncy
File 188:Health Devices Sourcebook 2001
         ECRI (A nonprofit agency)
File 187:F-D-C Reports 1987-2002/May W3
         (c) 2002 F-D-C Reports Inc.
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?t s11/9/1,2,3,4,6

11/9/1 (Item 1 from file: 442)
DIALOG(R)File 442:AMA Journals

00042939

Permeability of the Human Round - Window **Membrane to Cationic Ferritin**
(ORIGINAL ARTICLE)

GOYCOOLEA, MARCOS V.; MUCHOW, DAVID; MARTINEZ, GUMARO C.; AGUILA, PEDRO B.; GOYCOOLEA, HORTENSIA G.; GOYCOOLEA, CARMEN V.; SCHACHERN, PATRICIA; KNIGHT, WENDY
Archives of Otolaryngology
November, 1988; 114: 1247-1251
LINE COUNT: 00117 WORD COUNT: 01621
ISSN: 0003-9977
CORPORATE SOURCE: Accepted for publication July 19, 1988. From the Minnesota Ear, Head, and Neck Clinic (Dr M. V. Goycoolea) and the Otopathology Laboratory, University of Minnesota (Dr M. V. Goycoolea, Mr Muchow, and Mss Schachern and Knight), Minneapolis; The Chilean Military Hospital, Santiago (Dr Martinez); the Pathology Department, Hospital del Salvador, University of Chile, Santiago (Dr Aguila); and Audia Chile, Santiago (Drs M. V. Goycoolea and Martinez, Mr Muchow, and Mss H. G. Goycoolea and C. V. Goycoolea). Reprint requests to 5817 Merold Dr, Edina, MN 55436 (Dr M. V. Goycoolea). This study was supported in part by grant 5P50-Ns-14538 from the National Institute of Neurological and Communicative Disorders and Stroke, Bethesda, Md, by the 3M Co of Minnesota, St Paul, and by Audia Chile, Santiago.

ABSTRACT: An ultrastructural study was done in three sequential steps to determine if the **human round - window** membrane was permeable to macromolecules. Cationic ferritin was first placed for one hour in the **round - window** niche of two live rhesus monkeys. The same tracer was then placed in the same manner in two rhesus monkeys that had been dead for one hour. In both groups, cationic ferritin was observed to traverse the **round - window** membrane through pinocytotic vesicles into the scala tympani. After establishing that the transport capabilities of the **round - window** membrane of the monkey remained present one hour after death, cationic ferritin was placed for one hour in the **round - window** niche of two **humans** who had been dead for 30 minutes and one hour. The tracer was observed to traverse the **round - window** membrane through pinocytotic vesicles into the scala tympani in both **humans** . This report may be the first to document morphologically the permeability of **human round - window** membranes to macromolecules.
Animal experiments have shown that the **round - window** membrane, despite being three layers, behaves like a semipermeable membrane.
Antibiotics , (Ref. 1-7) antiseptics, (Ref. 8-9) local anesthetics, (Ref. 10,11) toxins, (Ref. 12) and albumin, (Ref. 13,14) placed in the **round - window** niche, can either be recovered in perilymph or observed to cause inner ear changes, such as hair cell damage. Morphologic demonstration that passage of substances from the middle to the inner ear can occur through the membrane has been provided by experiments in chinchillas, (Ref. 15) guinea pigs, (Ref. 16,17) cats, (Ref. 18) Mongolian gerbils, (Ref. 19) and rhesus monkeys. (Ref. 15) These studies have shown the passage of horseradish peroxidase, cationic ferritin, latex spheres, and/or neomycin-gold spheres as pinocytotic vesicles through the **round - window** membrane when placed in the **round - window** niche.
This has raised important questions as to the potential ototoxicity of otic **drops** and/or bactericidal agents used topically in the ear. At the same time, it has provided some basis for the assumption that otitis media can cause sensorineural hearing loss (Ref. 20) and perhaps endolymphatic hydrops, (Ref. 21) as a result of passage of noxious substances to the inner ear through the **round - window** membrane. It has also opened new

research avenues in developing the means of avoiding ototoxicity of topical **drugs** while preserving their therapeutic use, and also of developing the systems of controlled **drug** delivery into the inner ear. (Ref. 15)

However, despite the observations accumulated, there is no definite proof that otic **drops** are ototoxic when used to treat chronic otitis media, that otitis media is associated either with sensorineural hearing loss or endolymphatic hydrops, nor that what has been shown in animals occurs in **humans** .

The purpose of this study was to determine if the **human round - window** membrane was permeable to cationic ferritin. Based on the knowledge that the ultrastructure of the **human round - window** membrane is very similar to that of rhesus monkeys, (Ref. 15) this experiment was done in the following sequential steps:

1. Rhesus monkeys (normal, group 1). Cationic ferritin was placed for one hour in the **round - window** niche of normal live animals, accessible to the outer middle ear epithelium. Passage through the membrane was evaluated.
2. Rhesus monkeys (dead for one hour, group 2). Cationic ferritin was placed as in group 1. Passage through the membrane was evaluated and compared with that of the normal live monkeys in group 1.
3. **Humans** (dead for 30 minutes and one hour, group 3). Cationic ferritin was placed as in the monkey groups. Passage through the membrane was evaluated and compared with that of normal live and dead monkeys in groups 1 and 2.

MATERIALS AND METHODS

Rhesus Monkeys (Normal)

Two healthy adult monkeys (group 1) were used. They were anesthetized with pentobarbital sodium (30 mg/kg). After a tracheostomy had been performed, the middle ear was exposed using the transcanal approach (both ears were exposed). After the **round - window** niche was identified, cationic ferritin (0.1 mL) (Sigma Chemical Co, St Louis) was placed in the niche using a micropipet and left for one hour. The middle ear cavities were then injected with 4% glutaraldehyde in 0.2-mol/L phosphate buffer, pH 7.2. After the animals were decapitated, the temporal bones were removed and trimmed of excess bone and tissue. Two pin-sized holes were made in the cochlea: one at the helicotrema and the other in the scala tympani, approximately 2 mm apical from the **round window** . The cochleas were fixed with Karnovsky's solution, which was injected through the basal hole. Bones were rinsed and postifixed in 1% osmium tetroxide in 0.15-mol/L phosphate buffer at pH 7.2, for two hours at 4 degrees C. After several buffer rinses, the **round - window** membranes were removed. **Round - window** membranes were dehydrated and embedded separately in epoxy resin (Epon 812). Sections of 20 through 40 nm were cut with glass knives using an ultramicrotome (LKB Ultratome), mounted on enamel (Formvar)-coated single-slot or 50-mesh copper grids, stained with alcoholic uranyl acetate-lead citrate, and examined with an electron lmicroscope (JEOL 100 CX).

Rhesus Monkeys (Dead for One Hour)

Two previously healthy adult monkeys (group 2) that had been dead for one hour were used. Cationic ferritin (0.5 mL) (Sigma Chemical Co) was injected transtympanically into the middle ear cavity and left for one hour. The middle ear cavities were then injected with 4% glutaraldehyde in 0.2-mol/L phosphate buffer, pH 7.2, and the temporal bones and **round - window** membranes were removed and processed as in group 1.

Human Group (Dead for 30 Minutes and One Hour)

Two individuals (group 3) who had been dead for 30 minutes and one hour were studied. Cationic ferritin (0.5 mL) (Sigma Chemical Co) was injected transtympanically into the middle ear cavity and left for one hour. The middle ear cavities were then injected with 4% glutaraldehyde in 0.2-mol/L phosphate buffer, pH 7.2; the temporal bones were removed and processed as in groups 1 and 2.

RESULTS

Rhesus Monkeys (Normal)

After one hour of exposure to cationic ferritin, the tracer was found to be present in the three layers of the **round - window** membrane and in the perilymph immediately adjacent to the inner epithelium. Within the outer epithelial cells, ferritin was found within cells and between outer epithelial cells (Fig 1). In the connective tissue layer, ferritin was commonly observed within cell cytoplasms (Fig 2). Ferritin was also found in the inner epithelial cells and occasionally in the scala tympani (Fig 3).

Rhesus Monkeys (Dead for One Hour)

After one hour of exposure to cationic ferritin, the tracer was found at the same locations as in group 1 (Figs 4 through 7). However, ferritin was not found within cells in the connective tissue.

Human Group (Dead for 30 Minutes and One Hour)

Ferritin was observed in the three layers and in perilymph as in the monkey groups. Within the outer epithelial cells, ferritin was found within the cells (Figs 8 and 9) and between outer epithelial cells. In the connective tissue, ferritin was commonly observed in clumps immediately medial to the outer epithelial cells (Fig 10). Ferritin was also found in the inner epithelial cells and occasionally in the scala tympani (Figs 11 and 12).

COMMENT

The purpose of having done a systematic series of animal experiments on **round - window** membrane structure, function, and permeability (Ref. 15) has been to obtain information that would allow us to understand what occurs in **humans** . Our studies have involved the use of rodents (chinchillas), (Ref. 15) felines (cats), (Ref. 18) and primates (rhesus monkeys). (Ref. 15) We have made special efforts to use reduced but significant numbers of animals to answer specific questions. The methods have been, for the most part, morphologic, and, therefore, visible (utilizing light and/or electron microscopy) and permanent. This has limited the discussions to the methods, rationale, and the interpretation of findings. After 12 years of methodic data collection in animals, we thought that our background on the subject justified **human** studies. We had already demonstrated that cationic ferritin placed in the **round - window** niche of normal live monkeys was incorporated by the **round - window** membrane, (Ref. 15) and that the normal ultrastructure of the **round - window** membrane of these monkeys of the Old World is very similar to that of **humans** . (Ref. 15)

In this study, we initially observed that cationic ferritin placed in the **round - window** niche of normal live rhesus monkeys for one hour was incorporated by the **round - window** membrane (group 1). We then observed that cationic ferritin placed in the same manner in monkeys that had been dead for one hour was incorporated by the **round - window** membrane (group 2). These observations were suggestive that the metabolic capabilities of the **round - window** membrane remain present one hour after death. Based on these observations, cationic ferritin was placed in the **round - window** niche of **humans** who had been dead for 30 minutes and one hour. The observation that cationic ferritin is incorporated by the normal **round - window** membrane of **humans** 30 minutes and one hour after death suggests that the **human round - window** membrane is permeable to this tracer molecule. It is noteworthy that this occurs even one hour after death.

To our knowledge, this report is the first to document morphologically the permeability of **human round - window** membranes to macromolecules.

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00042838

Changes of the Permeability of Round Window **Membrane in Otitis Media** (ORIGINAL ARTICLES)

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ABSTRACT: The effects of endotoxin, exotoxin, and otitis media on the permeability of the **round window** membrane (**RWM**) in chinchillas was investigated by detecting tetraethylammonium chloride, applied to the **RWM** , using a potassium-selective micro-electrode in the scala tympani. The **RWM** , 48 hours following the application of endotoxin or exotoxin, became significantly more permeable to tetraethylammonium chloride than the normal **RWM** . Two weeks after the obstruction of the eustachian tube, the permeability of the **RWM** was decreased. These results suggest that bacterial toxins and the consequential migration of chemical inflammatory mediators act as promotive factors of **RWM** permeability, and that a pathologic thickness of the RMW and the presence of effusion induced by the obstruction of the eustachian tube acts as an inhibitory factor. In the clinical role of **RWM** permeability in **human** otitis media, these two factors must be taken into consideration.

Sensorineural hearing loss clinically observed in otitis media is thought to result from inflammatory and immunologic effects of the middle ear, and/or the secondary effects of **antibiotics** concomitantly applied to the middle ear cavity. n1-3 Many animal studies have documented the permeability of the **round window** membrane (**RWM**), in which several substances of different molecular size were applied to the **RWM** , and biochemical, histopathologic, and electrophysiologic investigations of the cochlea were performed. n4-13 These findings indicate that the **RWM** can be one of the critical factors determining the influence of bacterial toxins and chemical mediators in otitis media and **antibiotics** administered for otitis media on the cochlear function. However, studies of the permeability of the RMW under various pathologic conditions are limited, as sensitive methods to measure them have not as yet been developed. Recently, a direct observation of the inner ear fluid flow was made by measuring the activity of tetramethylammonium or tetraethylammonium chloride (TEA) ions with potassium (K+)-selective microelectrodes. n14, n15 The principle of this technique is to detect the spread of these substances using the high detectability of K+ microelectrodes against them.

Our animal experiment examined the change in the permeability of the **RWM** induced by endotoxin, exotoxin, and otitis media using this method.

MATERIALS AND METHODS

Healthy chinchillas weighing 450 to 550 g were used for this study. These animals were divided into four groups. Groups 1 (n = 6) and 2 (n = 5) were given applications of 100 mg of endotoxin from Escherichia coli

(serotype 0111:B4, Sigma Chemical Co, St Louis) and 50 mg of exotoxin from Staphylococcus aureus (Sigma), respectively, dissolved in 1 mL of Ringer's solution. For group 3 (n = 4), the surgical obstruction of the eustachian tube was performed according to a previous report. n16 Group 4 (n = 7) was the control group, receiving no treatment. The permeability of the **RWM** was measured 48 hours after treatment in groups 1 and 2, and after two weeks in group 3. Each animal was anesthetized with intramuscular injection of ketamine hydrochloride (20 mg/kg). The animals received artificial respiration through the tracheal cannula. Gallamine triethiodine (6 mg/kg) was given intramuscularly for muscular relaxation. The labyrinthine part of the bulla was exposed and the fluid surrounding the **RWM** and ossicular chain was cleared away as completely as possible. A small hole was then made 2 mm from the ridge of the **round window** at the scala tympani of the basal turn. A single-barreled K+-selective microelectrode was inserted into this hole and a chemical bond was used as a seal around the K+ microelectrode. After the microelectrode potential became stable, 150 mM TEA was applied to the **RWM** . The microelectrode was connected to a high-impedance dual electrometer (FD-223, WPI) via a silver-silver chloride wire, and the output was continuously recorded on a strip chart recorder. The indifferent electrode was a calomel half cell connected via a potassium chloride/agar bridge to a saline-soaked cotton wick placed on exposed neck muscles.

The fabrication and calibration methods of K+ microelectrodes was described elsewhere. n17-22 The K+ microelectrode thus made had an average slope of 52.8 +/- 1.9 mV per decade K+ activity difference and a K+ selectivity coefficient of 504 +/- 196 (n = 8) against TEA ions at 1 mM. The results expressed as means +/- SD were analyzed by Student's or Welch's t tests, and $P < .05$ was defined was a significant difference.

RESULTS

Figure 1 shows a representative trace of the potential change of the K+ microelectrode in normal animals. Two parameters were selected for analyzing the permeability of the **RWM** in this study. The first was the time (minutes) between the application of TEA to the **RWM** and the onset of potential change. This shows the arrival time when TEA penetrated into the **RWM** and was diffused in perilymph to reach the tip of the K+ microelectrode. We assumed the volume flow of the perilymph to be the same in each animal. Since the diffusion time in perilymph could be constant because of a constant distance between the **RWM** and the tip of the K+ microelectrode, the permeability of the **RWM** was the determinant of this period of time.

The second parameter was the slope (millivolts per minute) of the K+ microelectrode response. The response curves were found to elevate at an approximately constant rate a few minutes after the onset of elevation. This slope was thought to be dependent on the amount of TEA, penetration of the **RWM** . n23

Figure 2 shows the average time from the application of TEA to the arrival of the K+ microelectrode. Endotoxin applied to the middle ear significantly decreased this arrival time compared with the normal group ($P < .02$). The group given exotoxin showed a tendency to decrease arrival time and the group with otitis media tended to increase, but neither was significant.

Figure 3 shows the average slope of the K+ microelectrode potential. Both groups of endotoxin and exotoxin exhibited a significant increase of the slope ($P < .01$). On the other hand, a tendency to depress the potential slope was recognized in the otitis media group, although it was not significant.

COMMENT

Bacterial toxins, including exotoxin and endotoxin, have been proposed as important factors in inducing secretory otitis media and inner ear damage. n1, 5, 9, 24-28 Our study suggests that bacterial toxins cause the potential increase of the permeability of the **RWM** against the middle molecular substance, TEA (molecular weight, 165.7). It is interpreted that disruption of the permeability barrier function of the plasma membrane in the **RWM** due to bacterial toxins per se and/or secondary effects of

chemical mediators such as prostaglandins and catecholamines may lead to increased **RWM** permeability. n29-31 These findings indicate that bacterial toxins in the middle ear cavity probably promote primary and secondary damage to the inner ear across the **RWM** . Endotoxin used in this experiment was extracted from E coli. Although great similarities exist among the lipid moieties of endotoxin from various microorganisms, the chemical and biological heterogeneity of endotoxin is not identical. n32 Therefore, the investigations, with endotoxin extracted from gram-negative bacteria eliciting otitis media, may provide a critical supporting observation to our study. Furthermore, the identification of ototoxic substances, which are factors in sensorineural hearing loss secondary to otitis media, remains unresolved and further studies are required.

In experimentally induced otitis media, the permeability appeared to be reduced, which agreed with the results of the experiment using horseradish peroxidase. n13 Morphologic alterations, such as the thickening of the **RWM** or the residual effusion in the **RWM** was suggested by Schachern et al, n13 are considered to inhibit the passage of TEA to perilymph. The coexistence of promotive factors such as bacteria and chemical mediators, and inhibitory factors such as pathologic changes of the **RWM** and middle ear effusion will complicate the permeability change of the **RWM** in **human** otitis media.

We conclude that bacterial toxins promoted the permeability of the **RWM** and that otitis media made by the mechanical obstruction of the eustachian tube showed the opposite effect.

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11/9/3 (Item 3 from file: 442)

00036151

Thickness of the Human Round Window **Membrane in Different Forms of Otitis Media** (ORIGINAL ARTICLE)

SAHNI, RANA S.; PAPARELLA, MICHAEL M.; SCHACHERN, PATRICIA A.; GOYCOOLEA, MARCOS V.; LE, CHAP T.
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ABSTRACT: The thickness and morphologic characteristics of the **round window** membrane were evaluated in temporal bones from normal subjects as well as those with serous otitis media, purulent otitis media, and chronic otitis media. Temporal bones were studied in chronological order in six age ranges to determine the possibility of age-related differences. No significant difference in the mean thickness of the **round window** membrane was observed in terms of age groups in normal temporal bones or temporal bones from patients with otitis media; however, a significant difference in the mean thickness was observed in the various forms of otitis media compared with the normal **round window** membrane in all age groups. The membrane was thickest in patients with chronic otitis media when compared with that in normal subjects or those with serous or purulent otitis media. The epithelial layer (including the subepithelial space) and the fibrous layer were measured individually to determine in which layer the change in mean thickness occurred. These measurements showed an involvement of all layers of the **round window** membrane in those groups with otitis media, with maximal involvement of the combined epithelial layer and subepithelial space.

The physiologic role of the **round window** membrane as a phase differential in permitting labyrinthine fluid to move under the influence of the stapes is widely accepted. (Ref. 1-3) It is the process of diffusion through the **round window** membrane, however, that has attracted the attention of various investigators, and it is thought to be one of the important mechanisms resulting in sensorineural hearing loss due to involvement of the inner ear in the presence of otitis media.

A number of diffusion studies have indicated the permeability of the **round window** membrane to such substances as isotopes, (Ref. 4,5) **antibiotics** , (Ref. 6,7) anesthetics, (Ref. 8,9) proteins, (Ref. 10,11)

and toxins. (Ref. 12) Since the thickness of the **round window** membrane may affect its ability to act as a barrier between the middle and inner ear, a study determining the thickness of the normal **round window** membrane is essential. Although Dean and Wolff (Ref. 13) reported the thickness of the **round window** membrane to be 0.065 mm, they did not determine the thickness on an age-related basis. This is important in determining any changes in thickness that would occur due to the normal maturation of the membrane.

The histopathologic changes of the **round window** membrane in otitis media have been described as gradual and similar to those observed in the mucoperiosteum of the middle ear. (Ref. 14) These changes include an active wide subepithelial space (SES) as a consistent finding in all types of otitis media in animals and **humans** . (Ref. 15) Since an increase in the SES would result in an increase in the thickness of the **round window** membrane, a comparison of the thickness of the **round window** membrane during the various forms of otitis media should yield valuable information regarding the permeability of the membrane during otitis media. In this study we therefore determined the thickness of the **round window** membrane in both normal temporal bones and temporal bones from subjects with serous otitis media (SOM), purulent otitis media (POM), and chronic otitis media (COM), in six different age groups.

MATERIALS AND METHODS

Temporal Bone Processing

Temporal bones were removed with an oscillating bone plug saw at autopsy and placed in 4% phosphate-buffered formaldehyde solution. Following fixation, samples were defatted, decalcified, dehydrated, and embedded in celloidin. Temporal bones were sectioned horizontally from superior to inferior at a thickness of 20 mu m, and every tenth section was stained with hematoxylin-eosin. Selected sections were stained with resorcinol-fuchsin for identification of collagen and elastic tissue.

Sample Size and Analysis

The determination of sample size (the number of temporal bones used in each type of combination) was difficult to handle satisfactorily due to the following: (1) the multivariate nature of the problem; (2) the lack of prior knowledge leading to reasonable estimates of the outcome; and (3) the complexity in determining a meaningful alternative pattern. Hence, we decided to use the available temporal bones from each group. The decision was based on the availability of temporal bones harvested from autopsies at the University of Minnesota Hospitals, Minneapolis.

Data were evaluated on the basis of age as well as the degree to which the bones exhibited pathologic conditions (ie, temporal bones from patients with otitis media aged 1 to 5 years were compared with normal temporal bones from subjects 1 to 5 years old). Thirty-seven normal temporal bones, 23 temporal bones from the SOM group, 34 temporal bones from the POM group, and 55 temporal bones from the COM group were studied from six age groups (0 to 1 year, 1 to 5 years, 5 to 12 years, 12 to 30 years, 30 to 60 years, and 60 years onward).

Cross sections of the **round window** membrane where the niche and the membrane were at their widest were selected for the purpose of taking measurements. Temporal bones showing artifacts due to cutting angulation were excluded from the study. About three to five sections containing the **round window** membrane were available for study from each temporal bone. The thickness of the **round window** membrane was calculated from three different places. The first measurement was taken from the midpoint, and the second and third measurements were taken 0.2 mm from either side of the midpoint. The midpoint of the **round window** membrane was found by halving the distance between the tips of the crest of the cochlear fenestra supporting the membrane. A calibrated optical micrometer was used in the eyepiece of a light microscope, and all measurements were taken under X100 magnification. The mean thickness and SD were calculated from the above three measurements of the thickness of the **round window** membrane from each temporal bone studied. These measurements were compared in normal temporal bones and temporal bones with otitis media on the basis of age.

Fifty-two temporal bones with **round window** membranes 0.1 mm or

more in thickness and showing various types of otitis media were studied to measure the differential thickness of the individual layers. This measurement was selected as it was considered to be representative of the changes in the **round window** membrane in advanced cases of various types of otitis media. Since it was not possible to define a sharp zone between the external epithelial layer and SES of the **round window** membrane, the external epithelial layer and SES were measured together. A second measurement was taken from the middle fibrous layer and the inner layer combined. Similar measurements were also taken from ten normal temporal bones.

The final results were evaluated using analysis of variance and two-sample t tests. Results and significance of these measurements are discussed later.

RESULTS

Measurements of Thickness

The thickness of the **round window** membrane was calculated in 37 normal temporal bones in chronological order from the following age groups: 0 to 1 year, 1 to 5 years, 5 to 12 years, 12 to 30 years, 30 to 60 years, and 60 years and older (Table 1). No significant difference in the mean thickness was observed between groups in the normal temporal bones. Twenty-three temporal bones from the group with SOM, 34 temporal bones from the group with POM, and 55 temporal bones from the group with COM were also compared on an age-related basis. Likewise, no significant difference was seen between the age groups in temporal bones with SOM, POM, and COM, and they therefore are reported together. A statistically significant difference in the mean thickness of the **round window** membrane was observed in temporal bones with otitis media (SOM, POM, and COM) compared with normal temporal bones of the same age group ($P < .005$). The mean thickness of the **round window** membrane from normal temporal bones in all age groups was 0.0694 mm, and for the temporal bones from patients with SOM, POM, and COM was 0.0089 mm, 0.0956 mm, and 0.1141 mm, respectively. The mean thickness of the **round window** membrane was relatively greater in patients with COM in all age groups compared with the same age group of normal bones or those from patients with SOM or POM ($P < .001$).

Table 1. -- Mean Thickness of the **Round Window** Membrane in Normal Temporal Bones and Bones From Subjects With SOM, POM, and COM by Age

(SEE ORIGINAL SOURCE)

Fifty-two temporal bones representative of the various groups with otitis media, with a **round window** membrane thickness of 0.1 mm or more, and ten normal temporal bones were studied to measure the differential thickness of the individual layers (Table 2). This measurement was selected as it was considered to be representative of the changes in the **round window** membrane in advanced cases of various types of otitis media. Since it was not possible to define a sharp zone between the external epithelial layer and the SES of the **round window** membrane, the external layer and the SES were measured together. The mean thickness of the epithelial layer plus SES of the **round window** membrane from ten normal temporal bones was 0.018 mm and the mean of similar measurements from the **round window** membrane of 52 temporal bones from the otitis media group was 0.0562 mm. The mean thickness of the fibrous layer of the **round window** membrane from ten normal temporal bones was 0.0485 mm, and the mean thickness of the fibrous layer of the **round window** membrane from 52 temporal bones from the otitis media group was 0.0841 mm.

Table 2. -- Differential Thickness of **Round Window** Membrane

(SEE ORIGINAL SOURCE)

This indicated that otitis media increased the thickness of all layers of the **round window** membrane, ie, both the epithelial layer plus the SES as well as the fibrous layer. The increase in thickness of the epithelial layer and the SES, however, was greater or more pronounced than the increase in the thickness of the fibrous layer. The ratio of the thickness of the fibrous layer of the **round window** membrane to the epithelial layer plus the SES was calculated from each temporal bone in these two groups. The mean of these two ratios was 2. 11981 for the group

with otitis media, and 3.768 for the normal group. This indicated that the fibrous layer of the **round window** membrane is thicker in both groups: in the normal group the **round window** membrane is almost four times thicker than the fibrous layer; in the group with otitis media it is about two times thicker. These calculations were significant, by two-sample t tests, $P < .05$.

Morphology

Both the external epithelial layer and the middle connective-tissue layer of the **round window** membrane were hypertrophic in the groups with otitis media compared with the normal group (Fig 1). The inner mesothelial layer could not be identified under the light microscope in the majority of normal **round window** membranes and **round window** membranes with otitis media. A few round cells devoid of their nuclei were seen in the proximity of the inner layer of the **round window** membrane in some of the normal bones and in those with otitis media. These were possibly due to autolysis resulting from disintegration of the nucleus of the mesothelial cells. In a number of cases of otitis media, especially POM and COM, nucleated cells (polymorphonuclear leukocytes, plasma cells, and monocytes) were seen close to the inner layer of the **round window** membrane in the scala tympani.

Mucosa from the niche showed epithelial hyperplasia and metaplasia with marked hypertrophy of the SES and increased vascularity in the groups with otitis media (Fig 2). In patients with COM, subepithelial fibrosis was observed in the mucosa of the middle ear and of the **round window** niche (Fig 3). The thickness of the **round window** membrane in patients with otitis media was mostly due to hyperplasia and metaplasia of the external epithelial layer and the middle connective-tissue layer. Subepithelial hyperplasia was not as pronounced in the **round window** membrane as in the mucosa of the niche of the same temporal bone in the groups with otitis media.

Changes such as increased vascularity and widening of the SES were observed to be more intense in the mucosa of the niche than in the **round window** membrane. The fibrous layer of the membrane was observed to have a more organized distribution of collagen and elastic fibers than the tympanic mucoperiosteum. Blood vessels were seen in the SES of the **round window** membrane, their numbers decreasing considerably toward the inner layer. Blood vessels close to the inner layer were seen in some temporal bones, even in normal subjects. Increased vascularity was seen in the SES of the **round window** membrane in patients with otitis media. Distribution of elastic tissue in the connective-tissue layer was observed to be dense toward the scala tympani and central part of the **round window** membrane. The **round window** membrane was seen to have more collagen bundles than elastic fibers at its peripheral attachment.

COMMENT

The objective of this study was to determine changes in the thickness and structure of the **round window** membrane in the various forms of otitis media compared with normal bones. To find any age-related differences in the **human round window** membrane, a light microscopic study was performed in normal temporal bones and temporal bones with otitis media in chronological order of their age. There was no significant difference in the mean thickness of the **round window** membrane in normal temporal bones between the age groups. Also, no significant difference on the basis of age was observed in the **round window** membrane within any type of otitis media. In POM, age group 5 to 12 years, the thickness of the **round window** membrane was 0.0633 mm. Only three temporal bones were studied in this category, as additional temporal bones from subjects with POM in this age group were not available at the time of this study. The difference in the mean thickness observed in this age group compared with other age groups with POM may be explained by the smaller number of bones representing this subgroup and possibly an overlap between the types of otitis media. It has been shown in the past that otitis media can occur along a continuum, and one type of otitis media can evolve into another. (Ref. 16)

Su et al (Ref. 17) examined normal **human** temporal bones and measured

the transverse diameter of the **round window** membrane and the width and depth of the **round window** niche in all age groups. They did not find any increase in the size of these measurements with age, and they suggested that the otic capsule was fully mature at birth. They did not, however, measure the thickness of the **round window** membrane. The results of this study showed no significant difference in the thickness of the **round window** membrane on an age-related basis either in normal temporal bones or within any of the three groups with otitis media. Also, no differences in the histologic characteristics of the **round window** membrane were observed on the basis of age within the individual groups either in normal temporal bones or in temporal bones from subjects with otitis media, indicating complete maturity of the **round window** membrane at birth. This suggests that age offers no resistance in the permeability of the **round window** membrane in the presence of otitis media.

A significant difference in the thickness of the **round window** membrane between the four groups was observed (normal, 0.0694 mm; SOM, 0.0889 mm; POM, 0.0956 mm; and COM, 0.114 mm). This increased thickness in the groups with the more chronic conditions was due to hypertrophy of the external epithelial and connective-tissue layer and a widening of the SES. Epithelial hyperplasia and vascularity of the SES of the **round window** membrane were seen in temporal bones with all types of otitis media. White blood cells, essentially monocytes and lymphocytes, were seen close to the inner layer of the **round window** membrane and in the scala tympani itself in a number of ears with otitis media.

Inflammatory cells have been described as invading all layers of the **round window** membrane in experimentally induced otitis media in animals. (Ref. 14) Erythrocytes and leukocytes have been described to escape by increased permeability of capillaries of the SES of middle-ear mucosa. (Ref. 16) In an ultrastructural study of the mucosa of the middle ear in patients with otitis media, Lim and Brick (Ref. 18) described thickened multilamellar ligament of the subepithelial capillaries and morphologic evidence of increased vascular permeability. They also observed perforated pores and pinocytotic vesicles in the endothelium of the capillary wall, and hypothesized the escape of leukocytes, erythrocytes, and serum proteins.

Cameron (Ref. 19) described the events of inflammatory reaction in tissue as consisting of two parts: (1) vascular changes establishing hemodynamic adjustment and alteration in vascular permeability and (2) changes in white blood cells. Hemodynamic adjustment has been described as evolving in a temporal sequence that involves arteriolar and venous dilatations, increased flow through widening arterioles and venules as well as opening of inactive capillary buds, and increased permeability of microvasculature (initiated by chemical mediators and increased hydrostatic pressure) with outpouring of plasma fluids. Escape of plasma proteins with large molecular weight has been explained by a theory of molecular sieving. It is conceivable that a similar mechanism for the passage of these products exists in the **round window** membrane. The exact mechanism of the passage of these noxious agents across the **round window** membrane to the scala tympani still remains a mystery; however, the protein horseradish peroxidase has been demonstrated to cross the **round window** membrane in guinea pigs by pinocytosis, (Ref. 10) and pinocytotic vesicles have been described to occur on both the middle-ear and inner-ear surfaces of the **round window** membrane in **humans** . (Ref. 20)

Changes in the mucosa of the niche are more intense than changes in the **round window** membrane of the same temporal bones in the groups with otitis media. The organized distribution of the connective-tissue layer in the **round window** membrane compared with the mucoperiosteum of the niche observed in this study further suggests a local defense system in the membrane that resists infection to a greater degree than does the mucosa of the niche. This intense response in otitis media by the mucosa of the niche, however, may contribute to exposure of the **round window** membrane to increased cellular activity and possibly cellular toxic products. The longer the disease process endures, the greater the damage to the **round window** membrane and possibly to the inner ear. This adds support to the importance of early detection and medical or surgical intervention in the treatment of otitis media.

On staining with special stains (resorcinol-fuchsin), the membrane is seen to have more collagen bundles than elastic fibers at its peripheral attachment. Elastic fibers are observed to be denser toward the scala tympani and in the central part of the **round window** membrane. Similar findings have been observed by Schachern et al (Ref. 21) in an electron microscopic study of the **human round window** membrane.

The mean thickness of the epithelial layer plus SES and the fibrous layer of the **round window** membrane from ten normal temporal bones was 0.018 and 0.0485 mm, respectively. The mean thickness of the epithelial layer plus SES and the fibrous layer of **round window** membranes from 52 temporal bones from groups with otitis media was 0.0562 mm and 0.0841 mm, respectively. This suggests that all layers of the **round window** membrane are involved in the groups with otitis media, but the changes in the epithelial layer and SES are most pronounced. The ratio of the mean thickness of the fibrous layer of the **round window** membrane to the epithelial plus subepithelial layers from ten normal temporal bones and 52 temporal bones from subjects with otitis media was 3.768 and 2.1198, respectively. The connective-tissue layer is almost four times the thickness of the epithelial layer and SES in normal temporal bones, and about twice the epithelial layer and SES in 52 temporal bones with otitis media, the fibrous layer being thicker than the epithelial layer and SES in both groups.

The significant difference in the mean thickness of the **round window** membrane in various forms of otitis media compared with the mean thickness of the normal **round window** membrane observed in all age groups ($P < .005$) in this study suggests a reparative process. This may be due to an increased rate of proliferation of fibroblasts and capillary buds and the subsequent deposition of collagen to produce scarring as a process of repair. The maximum thickness (0.114 mm) of the **round window** membrane was observed in the group with COM.

We previously presented evidence of both temporary and permanent threshold shifts of the basal cochlear turn in patients with POM and those with COM. (Ref. 22) It has been and continues to be our hypothesis that inflammation or the effects of inflammation pass into the inner ear, via the **round window** membrane, resulting in damage to the basal turn. This damage, which is difficult to measure in the higher frequencies, can grow and in subsequent years manifest as routinely measurable sensorineural deafness. It seems reasonable that a thin **round window** membrane will be more permeable than a thick **round window** membrane. Thus, a thick **round window** membrane may protect the cochlea in patients with COM. Many pathologic and anatomic variances will influence the role of the **round window** as a portal entry from the middle ear to the inner ear.

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The Permeability of the Round Window **Membrane During Otitis Media** (ORIGINAL ARTICLE)

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ABSTRACT: Studies of the permeability of the **round window** membrane (**RWM**) during otitis media are important because toxins and cellular components that occur in otitis media as well as pharmacologic agents used in treating the disease have the potential to cross the **RWM** and pass into the inner ear. Twenty-five cats were evaluated electron microscopically as to the passage of a tracer, horseradish peroxidase, through normal RWMs and RWMs three days, one week, and two weeks following eustachian tube obstruction. Passage at three days following obstruction was similar to passage through the normal **RWM** . Following one to two weeks of obstruction, the permeability of the membrane was drastically reduced. The reduction in permeability was probably due to (1) the presence of residual effusion overlying the membrane, (2) the presence of granulation tissue within the niche, and (3) a thickening of the **RWM** .

Studies of the permeability of the **round window** membrane (**RWM**) are important because of secondary damage to the inner ear that may result from disease in the middle ear. Toxins and cellular products and components that occur in otitis media, as well as pharmacologic agents used in treating the disease and thus found in the middle ear, all have the potential to cross the **RWM** and enter the inner ear. Studies in **humans** have demonstrated that both sensorineural hearing loss (Ref. 1-8) and endolymphatic hydrops (Ref. 9) can occur secondary to otitis media. It has been suggested that these complications occur because of the passage of toxic substances through a permeable **RWM** . Bactericidal agents used topically in otologic surgery have been reported to be ototoxic, as have components of otic **drops** used in treating otitis media or as a form of prophylaxis in patients with tympanostomy tubes. (Ref. 10-13) Studies in animals have demonstrated that **antibiotics** , (Ref. 14-16) local anesthetics, (Ref. 17-19) toxins, (Ref. 20,21) tracers, (Ref. 22,23) and even albumin (Ref. 24,25) placed in the **round window** niche can either be recovered in the perilymph or be observed to cause changes in the inner ear.

Although passage of tracers through RWMs has been documented, most of these studies have been done in normal RWMs or, in some studies, in membranes exposed to very early changes of otitis media. The purpose of this study is twofold: (1) to evaluate the permeability of the normal feline **RWM** to tracers applied at various intervals, to assess the relationship of time of exposure to rate of passage; and (2) to evaluate the permeability of the **RWM** in cats with experimentally induced otitis media for three days to two weeks, to determine the relationship between pathologic changes in the **RWM** and the rate of permeability.

MATERIALS AND METHODS

A total of 25 healthy cats weighing 2 to 3 kg each, both male and female, were used for this study. The 25 cats were divided into three groups and prepared for surgical examination of the **RWM** . Group 1 consisted of RWMs from nine normal cats with unobstructed eustachian tubes; group 2 consisted of RWMs from 12 cats with surgically induced obstructions of the eustachian tube; and group 3 consisted of three controls.

Group 1

Nine cats were evaluated to determine the rate of passage of horseradish peroxidase (HRP) through normal RWMs. One to two microliters of 6% HRP was carefully applied to the **RWM** of anesthetized cats for periods of 30 s (in three cats), two minutes (in four cats), and ten minutes (in three cats). Fixation and processing are described below, under

"Application of HRP and Processing of Tissues."

Group 2

Round window membranes from 12 cats were evaluated for the passage of HRP following mechanical obstruction of the eustachian tube. In four cats the eustachian tubes were obstructed for three days, in three for one week, and in five for two weeks. The application of the tracer HRP, in all cats with obstructed tubes, was for two minutes. Fixation and processing of the RWMs are described below.

Group 3

Round window membrances from the remaining three cats received physiologic saline solution minus HRP followed by incubation in a solution of p-phenylenediamine dihydrochloride and catecholdihydrochloride (PDCH,) HRP minus PDCH medium, or complete medium less hydrogen peroxide. Processing is described below.

Obstruction of the Eustachian Tube

Cats were anesthetized with 30 mg/kg of ketamine hydrochloride containing 1% acepromazine maleate. Following injection of 1 mL of lidocaine hydrochloride containing 1% epinephrine bitartrate into the soft palate, a midline incision was made to expose the eustachian tubal orifice. Sterile Silastic sponge was then packed into the eustachian tubes and the midline incision closed. Prophylactic procaine penicillin G was administered, 1 mL intramuscularly.

Application of HRP and Processing of Tissues

Cats were anesthetized with 30 mg/kg of ketamine hydrochloride containing 1% acepromazine maleate. A postauricular incision was made and the external ear deflected. The parotid gland was bluntly dissected and retracted and the temporal muscle cut to expose the tympanic bulla. An opening was made in the bulla to expose the **RWM** , and in those cats with experimentally induced otitis media, the effusion was removed by suction. A few microliters of 6% HRP (type 2) in physiologic saline solution was then placed on the **RWM** for periods ranging from 30 s to ten minutes (for specific times, see groups 1, 2, or 3 above). The middle-ear cavity was then flushed with 4% glutaraldehyde to stop the reaction, the cat killed by decapitation, and the bullae removed. The stapedial footplate was removed and the oval window and the cochlear apex fenestrated and perfused with the glutaraldehyde.

Fixation was continued by immersion in glutaraldehyde for one hour. The samples were washed in three changes of 0.1 mol/L of phosphate, pH 7.4, and one change of TRIS buffer, pH 7. 6, incubated for 30 minutes in PDCH solution, washed again in TRIS buffer followed by phosphate buffers, postfixed in 1% osmium tetroxide in 0.1 mol/L of phosphate for one hour, washed in phosphate buffer, dehydrated in a graded series of alcohol, and embedded in plastic resin (Medcast). Cross sections of the **RWM** were cut to 1 mu m thickness and stained with toluidine blue for evaluation under the light microscope. Adjacent sections 200 nm thick were stained, one with uranyl acetate alone, the other with uranyl acetate-lead citrate.

Evaluation of Samples

Samples in which the RWMs were artifactually disrupted were discarded from the study. A minimum of five ears were available for study in each group. In most cases, two samples were available from each ear. Because samples were perfused during processing, the presence of HRP within the scala tympani was not considered an indication of its passage through the **RWM** . To eliminate the possibility of artifact due to perfusion, products of HRP reaction were counted only if they occurred within the layers of the **RWM** . Samples were therefore assessed as "no passage" or "passage into layers one, two, and/or three." Sections 1 mu m thick of all samples were evaluated light microscopically using the double-blind method. Light microscopic results were reconfirmed at the electron microscopic level.

RESULTS

Group 1

Structure. -- The structure of the normal feline **RWM** has been described as consisting of three layers. (Ref. 26,27) The tympanic surface is squamous cells one to two layers thick with multiple desmosomes and tight junctions atop a continuous basal lamina. The intermediate layer contains collagen and elastic tissue as well as capillaries and nerves. The inner labyrinthine layer consists of flattened, elongated squamous cells. The basal lamina is discontinuous, and cellular junctions are tight and lack desmosomes. Our ultrastructural findings generally agree with those described above; however, in this study, desmosomes were observed along the inner layer, as were gap junctions.

Permeability to HRP. -- Within 30 s following application of HRP, the tracer was observed in the first layer in one ear, in the second layer in two ears, and in the third layer in one ear (Fig 1). The tracer entered the cells by micropinocytosis (Fig 2) and was later found within the intercellular spaces (Fig 3). Horseradish peroxidase was observed within the intercellular spaces but was not observed within the tight junctions (Fig 4). Reaction product was observed within the capillary endothelial cells at this period in one ear. At two minutes after application, HRP was found in the first layer in two ears, in the second layer in two ears (Figs 5 and 6), and in the third layer in one ear. Ten minutes following application of the tracer, the reaction product was observed in the first layer in one ear, in the second layer in two ears, and in the third layer in two ears. In those ears in which the tracer entered the second layer, reaction product was intense on the epithelial basement membrane and the basal laminae of capillaries. Horseradish peroxidase reaction at all periods varied in intensity both from membrane to membrane and from cell to cell.

Membranes with two-minute applications were selected for comparison with RWMs from cats with experimentally induced otitis media because (1) there were fewer ears showing passage of HRP into all three layers at two minutes after application than at ten minutes; (2) since passage at 30 s and two minutes was similar, there would be less possibility of error with a longer postapplication period.

Group 2

Structure. -- Following three days' obstruction of the eustachian tube, a clear effusion in the middle ear was grossly observed in four ears, and a thin purulent effusion in the remaining ear. Edema of the subepithelial space occurred in all ears but one and infiltration of polymorphonuclear leukocytes (PMNs) was observed in the subepithelial space of the **RWM** in the ear with a purulent effusion in the middle ear. One week after obstruction, a thin purulent effusion in the middle ear was seen in four ears, and in two ears no effusion was observed. Edema of the subepithelial space was found in five ears, and infiltration of PMNs occurred in the four ears with effusion. Breaks in the epithelial layer caused by extruding PMNs were seen in two ears.

At two weeks after obstruction, a thick cloudy fluid and granulation tissue were observed in the middle ear cavity of all eight ears. The RWMs were severely thickened and contained polypoidal invaginations into the **round window** niches. Granulation tissue filled the **round window** niche, partially covering the RWMs. Platelets were observed within the capillaries, and the subepithelial space was edematous and contained abundant infiltration of PMNs and plasma cells, the plasma cells predominating. Edema and thickening of the inner labyrinthine layer occurred in seven ears, with inflammatory cell infiltration in five. Breaks in the epithelial membrane were seen in three ears.

Permeability to HRP. -- Three days following obstruction of the eustachian tube, HRP was observed within the first layer in three ears (Figs 7 and 8), in the second layer in one ear, and in the third layer in one ear. The intensity of reaction varied both from membrane to membrane and from cell to cell. By one week following obstruction, the tracer did not enter the **RWM** in five of the six ears (Fig 9). The one ear in which the HRP was seen in the first layer was the only ear of the group that did not have an effusion in the middle ear. At two weeks following obstruction, no HRP was observed in any layer of the **RWM** in seven of the eight ears (Fig 10). In the one ear in which HRP was observed, reaction product was only seen within one cell of the outer layer. Tracer was not observed in

the tight junctions in any ears with pathologic conditions. In those ears in which the tracer entered the **RWM** , it did so by pinocytotic activity. The tracer was not observed to enter the **RWM** by any other mechanism, even in areas of epithelial breaks.

Group 3

Structure. -- The structure of the **RWM** in the control ears was similar to that observed in the normal RWMs to which HRP had been applied.

HRP Permeability. -- Reaction product of HRP was not observed in the ears in which either Hankers-Yates' solution or hydrogen peroxide was eliminated from the incubation medium. Positive reaction was observed on red blood cells and within capillary lumens in the saline solution-treated control ears.

COMMENT

Previous studies of the passage of HRP through the normal RWMs had animals killed at times ranging from five minutes to 24 hours following application of the tracer. Tanaka and Motomura (Ref. 22) found the reaction restricted to the epithelial cells after five minutes and within occasional cells of the inner layer 40 minutes after application. In this study, HRP was observed within the epithelial cells 30 s after application and was even found within the inner layer of the membrane in one cat. The speed with which the HRP entered the **RWM** is not surprising because pinocytosis is known to be an extremely fast process.

Permeability to the tracer following one or two weeks of tubal obstruction was drastically reduced when compared with that in normal cats and those obstructed for three days. We believe that this reduction in permeability was probably due to three factors: (1) the protection afforded the **RWM** by the residual effusion overlying the membrane; (2) the thickening of the **RWM** due to infiltration of the subepithelial space by inflammatory cells and the formation of granulation tissue within the membrane; and (3) the presence of mucosal membranes and granulation tissue within the **round window** niche. Even if a small amount of a substance did enter the membrane, it would probably be degraded, due to the large number of inflammatory cells. In experimentally induced otitis media in cats, light microscopic studies have shown that the **RWM** follows the changes of the mucoperiosteum of the middle ear. (Ref. 28) There is a gradual thickening and cellular infiltration of the connective tissue layer by cells capable of phagocytosing and/or secreting enzymes capable of degrading substances that might pass through the outer layer of the membrane. The outer layer also has metabolically active cells capable of serving as a first line of defense.

Although the decrease in the permeability of the **RWM** in this study was in cats and cannot be directly correlated with permeability of the **RWM** in **humans** , some parallels can be drawn. In a study of **human** temporal bones with chronic otitis media, granulation tissue was one of the most frequently observed pathologic tissues, and the **round window** niche was second only to the epitympanum in its distribution. (Ref. 29) The niche was described as being frequently obliterated by thick fibrous granulation tissue. These findings are similar to those observed in this study in cats. Furthermore, permeability in the feline **RWM** , when it occurred, was by micropinocytosis. Micropinocytotic vesicles have been reported on both surfaces in the **human RWM** . (Ref. 30)

Our results in cats suggest that in persistent otitis media, there is a decrease in the permeability of the **RWM** . This decrease in permeability would probably not affect the passage of those substances that are present within the membrane, such as toxic products from inflammation, but would affect those substances, such as **antibiotics** , that are placed in the middle ear. It would seem that **antibiotics** when administered in chronic otitis media would be less likely to enter the **RWM** . We currently are evaluating the passage of substances of different molecular size, charge, and pH. Establishing patterns and rates of permeability is important not only so that we might prohibit substances from crossing the membrane but also so that we might know those characteristics that will allow a substance to traverse the membrane for use in treating disorders of the inner ear.

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The Human Round Window **Membrane; An Electron Microscopic Study** (ORIGINAL ARTICLE)

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ABSTRACT: The normal adult **human round window** membrane was examined

by transmission electron microscopy. The membrane consists of the following three layers: (1) an outer squamous epithelial layer with an underlying basement membrane; (2) a middle fibrous layer containing collagen, elastin, fibrocytes, vessels, and nerves; and (3) an inner layer of mesothelial cells. Mucosal membrane veils that cover the **round window** membrane, forming "false" **round window** membranes, are also described. These membranes are also three layered, including (1) an outer epithelial layer with an underlying basement membrane, (2) a middle fibrous layer containing collagen, elastin, fibrocytes, vessels, and nerves, and (3) an inner epithelial layer with an underlying basement membrane. Ultrastructural differences between these two structures are discussed. (Arch Otolaryngol 1984; 110: 15-21)

The role of the **round window** membrane in cochlear physiology is fairly well established. However, we are only beginning to understand the significance of the membrane as a portal of entry from the middle of the inner ear. Various animal studies have been undertaken to investigate the ability of this membrane to serve as a portal. Radioactive isotopes (Ref. 1,2) and labeled proteins, (Ref. 2) **antibiotics** , (Ref. 3-5) toxins, (Ref. 6) and tracers are some of the substances that have been placed on the middle ear surface of the **round window** membrane and later collected from perilymphatic fluids. Histological (Ref. 4) and electrophysiological (Ref. 3) alterations of the cochlea following the application of **antibiotics** to the **round window** membrane add support to the theory that passage occurs through this membrane. In addition, recent studies have shown an increased permeability of **round window** membranes in animals with otitis media. (Ref. 6)

In a histopathological study of temporal bones from patients with otitis media, (Ref. 8) serofibrinous precipitate and inflammatory cells were observed to be mainly localized in the scala tympani near the **round window** membrane. In another study, an increased incidence of sensorineural hearing loss was demonstrated in patients with chronic otitis media when compared with controls in all age decades. (Ref. 9) These **human** studies help to substantiate the role of the roundwindow membrane as a portal.

Ultrastructural studies of guinea pigs, (Ref. 10,11) monkeys, (Ref. 10) cats, (Ref. 12) and chinchillas (Ref. 13) have described the **round window** membrane as a three-layered structure with (1) an outer cellular layer with an underlying basement membrane; (2) a middle connective tissue layer containing fibroblasts, fibrocytes, collagen, elastin, vessels, and nerves; and (3) an inner mesothelial layer with numerous desmosomes and micropinocytotic vesicles.

It is surprising, however, that little or no attention has focused on the ultrastructural characteristics of the **human round window** membrane. The only published study of the ultrastructure of the membrane of the **human round window** is one recent study in infants (Ref. 14) in which artifactual and methodological factors confuse the interpretation.This preliminary report represents the first description of the **round window** ultrastructural characteristics in the membrane in normal adult **humans** . It is hoped that other studies of this membrane will include normal ultrastructural features related to age as well as to comparative animal studies. Once this background of normal morphologic features is established, it will be possible to study the ultrastructure of the **human round window** membrane in various clinical otologic problems.

METHODS

Round Window Membrane

Nine **round window** membranes were harvested from six patients (five men and one woman) ranging in age from 46 to 82 years. These patients were free of any history of hearing complaint. Samples were fixed within four hours postmortem by injection of 4% glutaraldehyde in phosphate buffer (pH 7.2) into the middle ear cavity via the tympanic membrane. Temporal bones were removed, the middle ear cavities opened, and fixation continued by immersion overnight. The **round window** membranes, including the bony annulus, were dissected from the remaining otic capsule, decalcified by edetic acid and postfixed in 1% osmium tetroxide in 0.1M phosphate buffer

(pH 7.2). Following postfixation, samples were dehydrated in a graded series of ethyl alcohol and embedded in epoxy. Cross sections of **round window** membranes were cut at 1 mum and stained with toluidine blue for light microscopic observation. Ultrathin sections were stained with uranyl acetate and lead citrate and examined with an electron microscope.

Mucosal Membranes

Fifty **human** temporal bones fixed in formalin and embedded in celloidin were randomly selected from our collection and assessed by light microscopy for the presence of mucosal membranous veils or "false **round window** membranes" within the **round window** niche. Five additional samples from three patients (two men and one woman), ranging in age from 30 to 83 years and having no history of hearing complications, were processed for electron microscopic assessment of mucosal membranes by intratympanic instillation of 4% glutaraldehyde. Following postfixation in 1% osmium tetroxide, samples were dehydrated in a graded series of ethyl alcohol and embedded in epoxy. Thin sections were stained with ruanyl acetate and lead citrate and examined by transmission electron microscopy.

RESULTS

Round Window Membrane

Of the nine samples studied, two **round window** membranes did not contain an inner layer. Because this inner layer allows us to differentiate between a true **round window** membrane and a mucosal membrane, these two samples were discarded. The remaining seven samples, like those of the lower species previously described (Ref. 10-13) are composed of three layers: an outer epithelial layer, a middle fibrous layer, and an inner cellular layer.The membrane is thickest at its attachment to the otic capsule and becomes thinner centrally. The outer epithelial layer faces the middle ear cavity and is composed of one to two layers of squamous cells (Fig 1, top). Intercellular membranes are not smooth but form fingerlike interdigitations with those of adjacent cells. The cells of this layer consist of both light and dark cells; however, light cells are frequently covered by cytoplasmic extensions of adjacent dark cells (Fig 1, bottom). Both types of cells have a dense cytoplasm with numerous microvilli on the middle ear surface. The long axes of the nuclei lie parallel to the membrane's surface. Glycogen is occasionally observed within these cells.Cells are joined by zonula occludens, zonula adherens, and abundant desmosomes. Intercellular cisternae are frequently found below the level of the junctions. Micropinocytotic vesicles are observed opening on both cellular surfaces. A continuous basement membrane containing multiple involutions underlies this entire layer.

The middle layer (Fig 2) contains numerous fibrocytes, occasional fibroblasts, collagen, elastin, vessels, and nerves. The density of elastin increase near the inner ear surface. Vessels are located within this middle layer but lie beneath the middle ear epithelium. They are composed of a continuous endothelium surrounded by a pericyte and a continuous basal lamina. Endothelial cells contain micropinocytotic vesicles that open on both cellular surfaces. Both myelinated and unmyelinated nerves are found in this layer. These nerves are always surrounded by Schwann's cells, and the nerve bundles are frequently surrounded by fibrocytic processes.

The inner layer (Fig 3) consists of mesothelial cells. The nuclei are large and flat with the long axis lying parallel to the membrane's surface. The cell body and nuclei are not frequently observed because much of the inner layer is formed by the long cytoplasmic extensions of these cells. The cytoplasmic extensions from adjacent cells overlap. Cellular extensions are connected by gap junctions and numerous desmosomes. The cells are not always closely approximated to underlying cells but often contain points of desmosomal attachment between large intercellular spaces. Cells do not possess microvilli, but do contain numerous micropinocytotic vesicles that open on both cellular surfaces.

Mucosal Membrane

Ten of the 50 temporal bones examined contained mucosal membranous veils or "false **round window** membranes," completely covering the **round window** membrane, forming what appeared to be a second **round window**

(Fig 4, left). Electron microscopic assessment of these mucosal membranes revealed that they were similar to the true **round window** membrane in their three-layered structure; however, the mucosal membranes had several other structural differences.Unlike the inner layer of the **round window** membrane, which is composed of mesothelial cells that lack microvilli or an underlying basement membrane, the inner layer of mucosal membranes is composed of squamous cells that contain both microvilli and a continuous underlying basement membrane. Cuboidal cells containing ciliated epithelia and secretory cells are also observed in both the inner and outer layers of the mucosal membranes (Fig 4, center) but are not observed in the normal **human round window** membrane. The middle fibrous layer of the mucosal membranes contains fibrocytes, collagen, elastin, vessels, and myelinated and unmyelinated nerves as does the **round window** membrane. The vessels of the mucosal membranes, however, are not always located adjacent to the outer surface of the membrane, as in the normal **round window** , but are scattered throughout the middle layer (Fig 4, right).Elastin content is not as dense as that of the **round window** membrane, nor does it increase in concentration near the inner surface.

COMMENT

The **round window** membrane is located adjacent to the sinus tympani and within the **round window** niche. This niche forms a well in which various substances, including middle ear effusions, may collect. The presence of these effusions adjacent to the **round window** membrane has led some investigators to speculate that these substances may pass from the middle ear through the **round window** membrane and into the inner ear, and, in fact, passage of various substances through the **round window** membranes of animals has been documented. (Ref. 1-7) Since the **human round window** membrane ultrastructurally resembles that of the lower species previously described, it is reasonable to assume that they have similar permeability characteristics. Tanaka and Motomura (Ref. 7) have shown passage of horseradish peroxidase through the **round window** membranes of guinea pigs to occur by micropinocytosis. The presence of micropinocytotic vesicles opening on both cellular surfaces of the cells lining the middle ear surface, the inner ear surface, and the vascular endothelial cells suggest that the **human round window** membrane is capable of the same type of transport.

In **humans** , mucosal membranous veils often cover the **round window** membrane. The presence of these mucosal membranes adjacent to the surface of the **round window** membrane may affect the membrane's permeability. These mucosal membranes may inhibit diffusion by adding an additional barrier, thus protecting the **round window** membrane. Alternatively, they may enhance diffusion of middle ear effusions by entrapment of the effusion adjacent to the surface of the **round window** .

Recently, Miriszlai et al (Ref. 14) reported their results of a study of the **human round window** membrane in infants. Unfortunately, their results seem to be somewhat affected by technical difficulties and postmortem autolysis. Much of our early work was also hampered by technical difficulties. Technical problems such as removing fragmented portions of the **round window** membrane or mucosal membranous veils of the **round - window** niche caused us to reevaluate our first samples.

We found the **round window** membrane and mucosal membranous veils to be ultrastructurally similar. Only the inner and middle layers differed. The inner layer of the mucosal membranous veils contained either squamous or cuboidal cells with microvilli and a continuous underlying basement membrane. The inner layer of the **round window** membrane contained mesothelial cells lacking both microvilli and an underlying basement membrane. Without this inner layer, it is difficult to distinguish the **round window** membrane from a veil composed of mucous membrane. It is our opinion that the micrographs in the study by Miriszlai et al lack this inner cellular layer. We believe that the inner layer they depict is in fact an underlying fibrocyte of the middle layer. In our study, vessels of the middle layer of mucosal membranes were observed to be scattered and the elastin content sparse and not concentrated near the inner surface; while in the **round window** membrane, vessels were localized adjacent to the middle ear surface of the membrane and elastin content was increased near the membranes' inner surfaces. In one of the micrographs in the study by

Miriszlai et al, vessels can be seen scattered throughout the middle layer.They also describe the elastin content as sparse and the thickness of the membrane to be less than that in the cat. Although the features observed by Miriszlai et al seem to resemble mucosal membranes more than **round window** membranes, it is important also to consider age-related and pathological changes in any comparative reports.

Further study of the **human round window** membrane is essential for better understanding of cochlear physiology and of various otological diseases, such as otosclerosis, trauma, middle ear tumors, sudden deafness, otitis media, and effects of **drugs** on the middle ear, that may involve the **round window** niche or membrane, altering its normal morphological and physiological state.

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Treatment of Chronic Suppurative Otitis Media With Topical Tobramycin and Dexamethasone (ARTICLE)

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Objectives: To investigate the safety and efficacy of a topical combination of tobramycin and dexamethasone in a primate model of chronic suppurative otitis media (CSOM) and to explore the contribution of the added topical steroid for the treatment of CSOM. Design: Blinded, randomized, placebo-controlled trial. Subjects: Sixty juvenile cynomolgus monkeys randomized into the following 6 treatment groups of 10 monkeys each: 0.3% tobramycin (group 1), combined 0.3% tobramycin-0.1% dexamethasone (group 2), combined 1.0% tobramycin-0.33% dexamethasone (group 3), 0.1% dexamethasone (group 4), vehicle (group 5), and phosphate-buffered saline solution (group 6). Interventions: Chronic suppurative otitis media was established by inoculating the right ear with Pseudomonas aeruginosa. After 4 weeks of drainage, animals were treated according to the group assignment with 3 drops twice daily for 7 weeks. Hearing thresholds were monitored with repeated auditory brainstem response testing (ABR), and clinical response was monitored with repeated otoscopic examinations and cultures throughout the study. Cytocochleograms were evaluated for quantification of outer hair cell loss. Results: Rapid resolution of otorrhea and eradication of P aeruginosa occurred in all groups receiving tobramycin. The inclusion of dexamethasone accelerated the resolution of otorrhea and negative yields of cultures compared with tobramycin alone. Otorrhea and positive culture findings persisted in the groups not treated with topical antibiotic. Results of ABRs at 4 and 8 weeks and cytocochleograms for outer cell hair loss were not affected by drug administration. Perilymph samples collected at the end of the study showed no detectable tobramycin. Conclusions: Combined tobramycin-dexamethasone ear drops were safe and effective in the monkey CSOM model. Dexamethasone enhanced the efficacy of tobramycin. Arch Otolaryngol Head Neck Surg. 2000;126:165-173

TREATMENT of otorrhea through a perforation or ventilation tube is a challenge for clinicians. Often, common respiratory pathogens are isolated.1/ However, unlike otitis media behind an intact tympanic membrane (TM), pathogens such as Pseudomonas aeruginosa, Staphyloccocus aureus, and other gram-negative organisms commonly are found, likely gaining access to the middle ear (ME) via the external auditory canal.2/ Many commonly prescribed oral antibiotics are not effective against these more troublesome bacteria in otorrhea.3,4/

Ear and eye drops containing an antimicrobial agent, with or without an anti-inflammatory component, have commonly been used for the treatment of acute or chronic otorrhea. A survey of pediatricians revealed that 79% of the respondents prescribed topical medication for treatment of chronic suppurative otitis media (CSOM).5/ Another survey revealed that 84% of the otolaryngologists use ototopical preparations for otorrhea through a perforation, 94% in the presence of a ventilation tube, and 93% in a draining tympanomastoid cavity.6/ Eighty percent of otolaryngologists believed that the risk of sensorineural hearing loss (SNHL) due to infection was as great as or greater than that due to the topical agents. Despite this belief, 3.4% of the same respondents claimed to have observed ototoxic effects related to ototopicals.6/

The ototoxic effects of various systemically applied drugs are well

documented in the literature.7/ Whether topical aminoglycosides applied to an inflamed human ME are ototoxic remains controversial. Most of the data in support of ototoxic effects in humans are anecdotal case reports.8,9/ Only a few studies have looked at ototoxic effects in humans in a systematic way.10-12/ The small number of studies that relate topical treatment to hearing loss in humans probably results from the difficulty in differentiating the effects of coexisting chronic or recurrent infection from that of topical aminoglycosides, since both potentially affect hearing.9,10/

Until recently, no ototopical antimicrobial preparation had been approved by the US Food and Drug Administration (FDA) for treatment of otorrhea in the face of a nonintact TM. Clinicians managing chronic and recurrent otorrhea have used such preparations without an FDA-approved otic indication, after warning the patients or parents of the potential ototoxic effects. Because this preference is substantiated by these controversial reports, there is a greater need today to avoid the potentially ototoxic, untested, and unapproved ear drops and to provide clinicians with the better, nontoxic, effective alternatives for the topical treatment of CSOM.

A combination of tobramycin and dexamethasone is currently marketed as an eye drop; however, it has been prescribed without an FDA-approved otic indication by otolaryngologists for the treatment of otorrhea as well. We therefore conducted a study to investigate the efficacy and safety of topical tobramycin-dexamethasone in a primate model of CSOM due to P aeruginosa infection.12/ A second objective was to determine whether the addition of a topical steroid provided additional benefit to ultimate treatment outcome.

RESULTS

One of the animals was killed during the study, owing to an illness unrelated to the study protocol. When the code was broken at the end of the study, it was found to belong to group 6.

OTOMICROSCOPY

All of the animals had normal TMs and MEs at entry. After the inoculation with P aeruginosa, the right ears were confirmed to be draining during biweekly otoscopic evaluations. The differences between the study groups in the degree of drainage throughout the study, including the pretreatment and posttreatment periods, is illustrated in Figure 1. The drainage was present in more than 95% of the observations across all groups, before initiation of treatment. All study groups had an average of grade 3 corresponding to drainage at least filling the external ear canal. The amount of drainage remained constant for groups 4, 5, and 6 throughout the treatment period. However, there was a gradual decrease in drainage for the groups treated with drops that included tobramycin (groups 1, 2, and 3). In groups 2 and 3, the average score for drainage decreased in just 2 weeks to 2, corresponding to filling only the ME, and in 4 weeks to 1, corresponding to moisture in the ME. The rate of decrease in the amount of drainage was faster for groups 2 and 3 when compared with group 1. The average score for otorrhea in group 2 decreased to less than 1 by the fifth week of treatment and remained stable at that level for the remainder of the study. On the other hand, group 1 had a lower rate of decrease in the amount of drainage. Furthermore, the drainage increased in group 1 when the ear drops were discontinued at the end of the study.

CULTURE FOR P AERUGINOSA

Pseudomonas aeruginosa was isolated from ear cultures in 98% of the observations before initiation of the treatment. There were no differences in culture positivity for P aeruginosa between groups during the pretreatment period. The cultures continued to yield positive results throughout the treatment period for P aeruginosa for groups 4, 5, and 6 (Figure 2). On the other hand, the groups that received drops containing tobramycin, ie, groups 1, 2, and 3, had a rapid decrease in the percentage of ears with cultures yielding P aeruginosa. All of the ears in group 2 yielded negative culture findings after 3 weeks of treatment, and these remained negative for the rest of the study period. In group 3, the ears with culture-positive findings decreased rapidly to 20% in 1.5 weeks; however, complete eradication did not occur until another 4 weeks of treatment had passed. Group 1 had a gradual decrease across 6 weeks to reach 0% P aeruginosa in cultures. The cultures continued to yield negative

findings during the last week of the study, when ear drops were not administered. However, a relapse for P aeruginosa during the ninth week was observed in 2 of 6 ears in the interval between the end of treatment and killing.

ABR TESTS

The hearing thresholds of the right ears underwent ABR testing 5 times during the study. At entry, the right ears had average (<plus or minus> SD) hearing thresholds of 21.4 <plus or minus> 7.4, 27.6 <plus or minus> 7.6, 30.8 <plus or minus> 10.8, and 34.5 <plus or minus> 12.5 dB for click and 2000-, 4000-, and 8000-Hz stimuli, respectively. Perforating the TMs resulted in 29.0-, 31.8-, 25.9-, and 24.3-dB increases in the thresholds for click and 2000-, 4000-, and 8000-Hz stimuli, respectively.

The average hearing thresholds for each treatment group at baseline, postperforation, pretreatment, treatment-interval, and posttreatment ABRs are shown in Figure 3. There were no significant differences in the threshold shift with perforation between the groups. The average threshold change between the pretreatment and posttreatment ABRs were -9.25, 1.63, -6.38, 6.75, -1.38, and 9.00 dB for groups 1, 2, 3, 4, 5, and 6, respectively (Table 1). Overall, a small stimulus-specific change, a slight improvement in low-frequency stimulus, was observed with the administration of treatment. Groups treated with drops containing tobramycin with or without dexamethasone (groups 1, 2, and 3) did not have any significant worsening with the treatment. The number of ears with a difference of hearing thresholds between pretreatment and posttreatment equal to or exceeding an average of 10 dB was 5 in group 4, 4 in group 6, 2 in groups 3 and 5, 1 in group 2, and 0 in group 1. Only groups 4 (20.0- and 22.5-dB increases in 2 ears) and 6 (21.25-, 30.0-, and 50.0-dB increases in 3 ears) had any ears with at least a 20-dB threshold increase during the treatment period.

The left ears of 12 randomly selected animals underwent a single ABR test to determine the hearing thresholds of uninfected, untreated ears that subsequently underwent sampling for cytocochleograms. These left ears demonstrated hearing thresholds similar to the baseline thresholds of the right ears.

PERILYMPH FINDINGS

The correlation coefficient for the standard curve was 0.99. The accuracy for the individual quality control samples ranged from 81% to 105%, with an overall accuracy of 94%. Two of the samples were consumed during the development of the testing conditions that would yield maximum electrospray ionization response for tobramycin. Four samples were inadvertently damaged during the shipment. One analytical run was sufficient to assay all of the remaining 33 perilymph fluid samples. All of the samples of perilymph assayed below the limit of quantitation (both lower quadrants, <40 pg/uL) for tobramycin.

ME FINDINGS

Average scores for the degree of TM and ME inflammation determined by otomicroscopy are presented in Table 2. The uninfected, untreated left ears served as controls, with an average score of 0 for TM and ME. Groups 3, 4, and 6 had higher scores for inflammation. Group 1 had the lowest score among the infected study groups.

Histological assessment of the TM, ME, and mastoid mucosal thickness is summarized in Table 2. The thickness of the TM could not be assessed in 5 of 12 control group specimens because of technical difficulties related to the very thin TMs. Among the infected ears, the thickness of TM was the highest in group 5 and the lowest in group 2. Mucosal thickness of ME was the highest in group 6, followed by groups 4 and 5, and lowest in group 2, followed by groups 3 and 1. Mastoid mucosal thickness in group 2 was the lowest, followed by group 3.

COCHLEAR HISTOPATHOLOGICAL FINDINGS

The light microscopic evaluation demonstrated purulent material within 2 cochleae, 1 in groups 5 and 6 each. In those specimens, the inner ear structures were grossly identified; however, damage to the organ of Corti and significant loss of hair cells prohibited any count from being performed. The data of the 2 cochleae with pus are not included in the calculation of the average OHC loss(OHCL) of these treatment groups. The cytocochleogram revealed partial damage, probably as a result of

processing, in 2 other cochleae. The OHCs in the first coil of a cochlea in group 6 and all the OHCs except the first part of the first coil in another cochlea in group 5 could not be read. Only the data on undamaged sections of these 2 cochleae are included in the calculation of the averages of the treatment groups.

Results of light microscopy demonstrated normal basilar and Reissner membranes, stria vascularis, and organ of Corti (Figure 4, A). There was no damage to the inner hair cells (Figure 4, B and C). The OHCL did not show considerable differences between the various parts of cochleae (Table 3). The OHCL in the first coil was slightly higher than in the second coil, a finding consistent throughout the groups, including the control group. The average OHCL was 0.90%, 0.86%, 1.11%, 1.09%, 0.90%, 0.82%, and 0.65% of the total number of hair cells for groups 1, 2, 3, 4, 5, and 6 and the control group, respectively.

None of the cochleae in any treatment group, except the 2 with pus, had more than 3% OHCL. Although OHCL below the levels of 5% is considered insignificant, the distribution of the number of ears that had at least 1% and 2% OHCL in each treatment group are presented in Table 3. These results suggest no significant OHCL during the topical treatment of CSOM with tobramycin or dexamethasone.

COMMENT

The ethical and methodological limitations of obtaining reliable information on ototoxic effects in humans leads to research in animals. Most of the studies on ototoxic effects have been performed in chinchilla or guinea pig models.14-18/ Several studies in various animals have demonstrated hearing loss or cochlear damage due to ear drops. Various antibiotics, antifungals, and solvents penetrated the perilymph and produced hair cell loss in animals. When the same ear drops were placed into the ME of higher species, such as baboons, a more limited sensory cell loss was seen.19,20/ On the other hand, topical dosing of ciprofloxacin hydrochloride to chinchillas demonstrated no significant effect on ABRs or the cytocochleogram.21/ The outcome differences in these studies may result from active ingredients in the drops, duration of the treatment, degree of inflammation, and differences in size, thickness, location, and permeability of the round window membrane between species. Applicability of these safety results to humans, therefore, have been questioned.

The differences in human ME architecture has implications not only for safety but also for treatment efficacy. Studies on ototoxicity are rarely conducted in an infectious model. This results in part from the lack of a good infectious model in rodents. Significant anatomic interspecies differences in the external ear canal, eustachian tube, mastoid pneumatization, and access to mastoid from ME have limited the use of animals for efficacy studies. Mastoid involvement in human CSOM has been claimed to be a major factor in the chronicity. The restricted access between the ME and mastoid air cells was thought to limit the efficacy of ear drops. These concerns, besides the concerns about applicability of rodent safety results, support basic studies in primates. Therefore, a monkey animal model was developed by Dohar et al22/ to study efficacy and safety of ear drops in CSOM.

The primary reason for preferring a noninfectious model for evaluating safety is to test the ototoxicity of an ear drop when the ear is in its most vulnerable state. Although ear drops are typically prescribed to treat drainage, drops may be used after the resolution of drainage. The persistence of inflammation in the ME may continue to limit the penetration of drops into the perilymph. The undetectable levels of tobramycin in the perilymph in our study may reflect restricted permeability due to residual ME inflammation, despite presumed cure seen on otoscopy and culture findings. In our study, the degree of inflammation as assessed by mucosal thickness in the groups with persistent infection was up to 8 times that of the control side for the TM, 5 times that for the ME mucosa, and 3.5 times that for the mastoid mucosa. The degree of ME inflammation in our study appeared to be mainly due to infection. However, although the otorrhea had resolved before the end of the study in the groups treated with tobramycin-containing drops, inflammation (mucosal thickness) persisted in TM, ME, and mastoid mucosal specimens. Even in the group with the least degree of inflammation, group 2, TM thickness was 4 times and ME mucosa

thickness was 1.5 times the control side. The thickness of the mastoid mucosa in group 2 was the same as that of the control group. Group 1, however, had relatively higher average thickness at the time the animals were killed. The only group with recurrent P aeruginosa infection (group 1) had a similar amount of mastoid inflammation as the groups with persistent drainage. This is reflected in the thicker mastoid mucosa. On the other hand, some investigators linked the biofilm state of the bacteria with the persistence or recurrence in CSOM and other chronic infectious diseases.23/ These bacteria are distinct from their planktonic forms, very resistant to antibiotics and host defense mechanisms, and difficult to isolate using routine culture techniques. However, it is unclear, given this explanation, why only a few ears in group 1 had recurrence in our study.

In a study on susceptibility patterns of aural Pseudomonas isolates, Dohar et al4/ reported that tobramycin had significantly better in vitro activity (94%) compared with gentamicin (79%). Piperacillin sodium was the only intravenous agent with better (96%) in vitro activity. Our study clearly demonstrates the efficacy of tobramycin in the resolution of otorrhea and elimination of P aeruginosa. All 3 groups treated with tobramycin (groups 1, 2, and 3) had gradual resolution in the amount of otorrhea over several weeks, whereas there were no differences in the amount of otorrhea in the other 3 groups (groups 4, 5, and 6). Both groups receiving tobramycin-dexamethasone (groups 2 and 3) experienced more rapid resolution of otorrhea than did the group receiving tobramycin alone (group 1). These results may in part be consistent with the study by Fradis et al24/ that compared the efficacy of topical tobramycin and ciprofloxacin for the treatment of CSOM in humans. In their study, tobramycin (without dexamethasone) was found to be equally effective (66.7%) in bacteriologic response but worse in clinical response (72.2% vs 78.9%) when compared with ciprofloxacin ear drops. In another study, ototopical ciprofloxacin was found to be effective in nearly 70% of patients with otorrhea associated with P aeruginosa, previously unresponsive to other antimicrobials.25/ In a study of children with acute purulent otorrhea, topical ofloxacin demonstrated an 84.4% cure in subjects evaluated clinically, and it eradicated 96.3% of all baseline pathogens in subjects evaluated microbiologically.2/

Our study clearly demonstrates an added benefit of dexamethasone when combined with tobramycin for resolving otorrhea and eradicating P aeruginosa. The duration of treatment necessary to achieve complete eradication of P aeruginosa from the ears were 3, 5.5, and 6 weeks for groups 2, 3, and 1, respectively. Although not quite different than the 66.7% bacteriologic response reported with 3 weeks of topical treatment of human CSOM with ciprofloxacin or tobramycin in the study by Fradis et al,24/ prolonged need for treatment in the monkey model may result from less frequent (twice a day) administration of the drops, limited access of the dropped medications into the ME because of the narrow ear canals, and anticipated natural nonhygienic habits of monkeys that may lead to constant or recurrent contamination of their perforated ears.

Differences in the responses for culture and clinical outcome measures were observed in a previous study using this model.22/ In that study, a rapid eradication of P aeruginosa with topical ciprofloxacin, its vehicle, or Cortisporin (a combination product of hydrocortisone, neomycin sulfate, and polymyxin B sulfate) was not followed by a clinical response as assessed by otoscopy. Although the treatment period in that study was only 4 weeks, no decrease in the amount of otorrhea was observed. However, in our study, a response was apparent even in the first 4 weeks of the 7-week treatment period. In fact, for groups 2 and 3, the drainage score was halved in the first 2 weeks.

Monitoring of hearing loss is conducted when medications with potential ototoxicity are used in clinical practice or in animal studies. Hearing loss was monitored with ABR at 5 different stages throughout our study, to better identify, besides the histological features, the contribution of each of the potential factors, ie, TM perforation, otorrhea, duration of otorrhea, and ototoxicity. However, differentiation of SNHL from the conductive component resulting from perforation of the TM and otorrhea in animals is not trivial. The significant threshold difference between the first and the second ABRs in our study is consistent

with the conductive hearing loss due to the wide TM perforation. The otorrhea present in all of the animals during the third ABR was a component of the conductive hearing loss. Repeated widening of the TM perforations to maintain the exposure of the ME and the inner ear to the ear drops preserved the conductive hearing loss throughout the study. Although the conductive hearing loss is seen in the lower frequencies, the higher frequencies are those affected first by ototoxic agents.26/

When compared with the postperforation hearing thresholds, all of the treatment groups except group 6 had a slightly better hearing level at the end of the study. In group 6, however, the hearing was slightly worse than the postperforation levels. In a comparison of the average pretreatment and posttreatment hearing levels, the following 3 groups showed deterioration: group 2 by 1.63 <plus or minus> 4.30 dB; group 4 by 6.75 <plus or minus> 11.29 dB; and group 6 by 9.00 <plus or minus> 19.50 dB. When we looked at the individual ears, a total of 14 ears demonstrated at least a 10-dB deterioration, and 5 ears had at least a 20-dB deterioration in hearing during the treatment period. Three of the 5 ears with a 20-dB hearing loss belonged to group 6, and 2 were in group 4. The degree of worsening in the hearing in these 2 ears in group 4 were 20 and 22.5 dB, and in the 3 ears in group 6, 21.25, 30, and 50 dB.

The histological evaluation of the cochleae demonstrated purulent labrynthitis in 2 of the ears. Neither of these ears were in the groups that were treated with drops including tobramycin or dexamethasone. These data suggest that hearing loss or OHCL may be due to the infection. The degree of SNHL in humans has been found to correlate with the duration of chronic otitis media.27/ Presence of SNHL has also been found to be related etiologically to otitis media with effusion.28/ When effective medications are used, this complication of CSOM is rarely seen. This significant complication in our study reminds us of all the potential complications of CSOM, some of which are life threatening, and the importance of developing a safe and effective treatment for this condition.

The data on the OHCL did not include the 2 ears with labyrinthitis. If included, a 100% OHCL for those 3 ears would increase the average and the SD of the OHCL for those groups. These extreme values, although appropriate for the purpose of the analysis of the study, would obscure the homogenously low OHCL that was comparable to that of the other groups. Moreover, the OHCL in these 2 ears did not result from the ototoxicity of the ear drops, but, ironically, because their drops lacked any antibiotic or anti-inflammatory agent.

The OHCL results in our study were well below the accepted limits for ototoxic effects. Average OHCL up to 5% is considered normal.22/ Our study revealed an average OHCL of less than 1.11% in all treatment groups. None of the sections in any treatment group exceeded 1.78% OHCL in average. A comparison was made between hearing and the histological data in the ears that exceeded thresholds in hearing tests or OHCL, to assess whether there were individual correlations between these factors. In group 4, the ear that had 20-dB worsening had 2.36% OHCL, whereas the ear with 22.5-dB worsening had only 0.75% OHCL. In all of the other ears in group 4 that had at least a 10-dB hearing loss, the OHCL was less than 2%. One of the 2 ears in group 5 that had a 15-dB hearing loss was found to have 0.35% OHCL. The second ear with a 12.5-dB deterioration, however, was the ear that had damage in certain sections of the cochlea. However, the OHCL in the preserved sections was only 0.83%. The cochlea with pus in the vehicle group had significant hearing loss after the inoculation of the animal with P aeruginosa, but before the initiation of the treatment. The analysis of hearing loss and histological results for each individual animal with relatively outlying data did not demonstrate an ototoxic effect of tobramycin or dexamethasone.

A Pearson correlation analysis between OHCL and change in hearing with treatment in all of the animals did not demonstrate a statistically significant ($r = -0.12$; $P = .39$) relationship. It should be remembered that the data for cochleae with pus or with damaged sections were excluded from the initial analysis. To assess the effect of this on the correlation, 100% of OHCL was entered to the sections of missing data because of pus or damage. This brought the correlation coefficient to 0.33 at $P = .01$. It seems that the persistence of otorrhea and the chronicity of the

suppurative otitis media may increase the OHCL. The SNHL in some animals seems to be due to the infection itself. At least in the 2 cochleae with pus, this relationship is clear. The correlation between hearing and histological findings was analyzed separately only for the 3 groups that were given tobramycin. This correlation between hearing and OHCL for the groups was significant ($P = .03$) for groups 1, 2, amd 3. However, the correlation for these groups was negative ($r = -0.40$), suggesting that for groups that received tobramycin, more pronounced hearing loss was associated with less OHCL. This negative correlation may also mean that with the resolution of otorrhea, there was an improvement in hearing, but that this may be increasing the risk for OHCL. Although the degree of OHCL in this study was well below the thresholds for ototoxic effects, this slight trend is consistent with other studies that have demonstrated the effect of inflammation in reducing the risk for ototoxic effects.

Our study monitored ototoxicity, similar to other animal studies, by assessing the hearing loss and OHCL. This approach ignores potential vestibulotoxicity. No apparent signs of vestibulotoxic effects developed in any of the animals during the study period; however, a systematic and objective method of assessment was not part of the study protocol. Since many topical agents, such as aminoglycosides, may have prominent toxic effects on the vestibule, some while sparing the cochlea, standard test batteries should be developed to monitor vestibulotoxicity and included in the animal models for ototoxic effects.

Our study suggests that tobramycin with dexamethasone is a very effective treatment for otorrhea and eradication of P aeruginosa in a monkey CSOM model. When comparing the treatment groups for hearing threshold changes and OHCL, our study suggests that neither tobramycin nor dexamethasone is ototoxic, individually or in a combined formulation. Dexamethasone clearly contributes to the efficacy of the combination ear drop, leading to more rapid resolution of the CSOM and eliminating the risk of recurrence after the discontinuation of drops. The tobramycin-dexamethasone ear drop presents a promising choice for the treatment of otorrhea due to P aeruginosa infection. Future studies should address potential vestibulotoxicity of aminoglycosides as well as assess the safety and efficacy of this ear drop in humans.

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samples were obtained for cultures. The presence of the perforation was checked, and if the TM had healed, it was reperforated. If the size of the perforation was smaller than 50% of the TM area, it was enlarged. Reperforation of the TM was documented.

The ABRs were performed in a soundproof booth using a compact auditory electrodiagnostic system (Nicolet Instrument Corp, Madison, Wis) for stimulus generation and potential recordings. Two types of stimuli were presented: clicks and tone bursts of 2000, 4000, and 8000 Hz. For each stimulus, 2000 sweeps were recorded, analyzed, and stored. Stimulus intensity was decreased from 100 dB, in steps of 20 dB down to 40 dB, in steps of 10 dB down to 20 dB, and in steps of 5 dB down to the level of hearing threshold. When ABR potentials disappeared, the ABR was repeated at 5-dB increments until the potential disappeared. The level of hearing was then confirmed by obtaining the potential again at the 5-dB lower threshold.

After the sedation with ketamine hydrochloride (10 mg/kg), animals were killed using intraperitoneal injection of pentobarbital sodium (35mg/kg), followed by vital perfusion an hour later. Intracardiac perfusion with PBS for 3 minutes was followed by perfusion with Karnowsky fixation solution for 10 minutes. The temporal bones were dissected out within half an hour. The bony external ear canal was removed, and the TM thickness was graded (scale, 0-4+) using an operating microscope. Following removal of TM and malleus, the thickness of ME mucosa (scale, 0-4+) was assessed. Thicknesses were graded by the same investigator (C.M.A.), to have a subjective assessment of the differences between specimens. A punch biopsy specimen, including bone periosteum and mucosa, was obtained from the hypotympanum. The incus and stapes were removed and saved for histological examination. A separate bone and mucoperiosteal punch biopsy specimen was obtained from the mastoid, just peripheral to the antrum. The tissues were decalcified with 5% formic acid, embedded in paraffin, sectioned, and stained with hemotoxylin and eosin using standard techniques. The thickness of the TM and the mucosa of ME and mastoid were measured as an indicator of the degree of inflammation, using an image analysis package. Quantitative histological analysis was performed using a commercially available software (Metamorph Imaging System, Version 2; Universal Imaging Corporation, West Chester, Pa). Mucosal thickness was measured on the sections stained with hematoxylin and eosin. For each location, 3 measurements were randomly obtained, and their average was used in the analysis.

Immediately after the luxation of the stapes, the perilymph was aspirated through the oval window with a microliter pipette (Pipetman; Rainin Instrument Co, Woburn, Mass) and saved. The round window was punctured, and the labyrinth was perfused with fixative. Following trimming to remove the bone around the labyrinth, the cochleae were placed in the fixative in a refrigerator at 4 degreesC overnight. The cochleae were placed into cacodylate buffer and reperfused through the round window twice weekly until shipment to the Karolinska Institute, Stockholm, Sweden. There, the specimens were dehydrated and embedded in agar. They were processed in a routine manner for light microscopy and dissected for cytocochleogram.

On the day each animal was killed, the treatment code was broken and a perilymph penetration study was performed. The groups that had received drops with tobramycin during the treatment period were used for the study. The left ears of a few animals were included as controls. According to the

protocol, the treatment had been discontinued at least 1 week before the animals were killed. To assess the penetration of tobramycin through the round window membrane, 3 drops of 0.3% tobramycin were applied in vivo to the external ear canals, similar to the method used throughout the experiment. To detect any potential time dependence, the animals were divided into 2 groups, and perilymph samples were collected approximately 1 or 3 hours after the dosing. After the animals were killed and the temporal bone was dissected, the ME was irrigated thoroughly to wash out any remaining tobramycin. The ME was dried, and the stapes was luxated. A micropipette with a pipet tip was used to aspirate the perilymph. The sample volume was measured, and it was stored at 80 degreesC until the transfer and the analysis for the assay. To control for the effect of perilymph contamination from the ME during sampling, a group of left ears was dissected as described, and 3 drops of tobramycin were applied. The ME was irrigated and dried as in the experimental group just before obtaining the perilymph sample.

The perilymph samples were transferred to TexMS Analytical Services, Houston, Tex, for quantitative analysis of tobramycin. An internal standard was prepared with bekanamycin in perilymph fluid. Aliquots were analyzed by means of high-pressure liquid chromatography and mass spectrometry with electrospray ionization and selected ion monitoring. The protoneated molecular ions for tobramycin (mass to charge ratio, 490) and the internal standard bekanamycin (mass to charge ratio, 506) were monitored, and the resulting intensity ratio was used for quantitation. A 5-point calibration curve was then generated using control perilymph matrix spiked with tobramycin at 40, 60, 80, 100, and 120 pg/uL. Duplicate calibration standards were used at the high and low ends of the curve. Single standards were used for the 3 intermediate levels. Separately prepared perilymph samples spiked at 60 and 100 pg/uL were used as quality control samples and analyzed in duplicate.

A block-surface technique method described by Spoendlin and Brun13/ was used for the histological evaluation of ototoxic effects. Surface preparations were examined under light microscopy for the quantification of hair cell loss. The total number of outer hair cells (OHCs) and of damaged OHCs were counted in 4 parts (each coil in 2 parts). Hair cells were counted separately for each position (first, second, and third OHC rows) in each part of each coil. The results are reported as percentage of the damaged hair cells for each part of the cochlea.

MATERIALS AND METHODS

Sixty juvenile cynomolgus monkeys of both sexes were included in the study. The animals were quarantined for 4 weeks before the experiment. All animals were examined using an operating microscope and tympanometry to confirm the health of the TM and ME. The animals were assigned randomly (10 animals per group) to 1 of the following 6 treatment groups: group 1, 0.3% tobramycin; group 2, 0.3% tobramycin-0.1% dexamethasone; group 3, high-dose 1.0% tobramycin-0.33% dexamethasone; group 4, 0.1% dexamethasone; group 5, vehicle containing benzalkonium chloride; and group 6, phosphate-buffered saline (PBS) solution. Histological findings and auditory brainstem response (ABR) data on the uninfected, untreated left ears were collected and are presented as separate control data for comparison of normative data. Investigators and study personnel were blinded to the treatment group assignment. The procedures on animals were approved by the Animal Research and Care Committee at the Children's Hospital of Pittsburgh, Pittsburgh, Pa, and in accordance with the US Public Health Service Policy on Humane Care and Use of Laboratory Animals, the National Institutes of Health Guide for the Care and Use of Laboratory Animals, and the Animal Welfare Act.

STUDY DESIGN

This study enabled investigation of the efficacy and safety of tobramycin and dexamethasone at 2 different concentrations, as well as the components 0.3% tobramycin, 0.1% dexamethasone, and vehicle as separate treatments for the assessment of effects of each component on the outcome. A sixth group included as a negative control group was treated with PBS drops. Nonperforated, uninfected, and untreated left ears of 2 animals from each of the 6 treatment groups were preselected randomly for comparison with the treated ears. The ABRs were performed only once on the left ears in this group. Middle ear and perilymph samples were obtained and the

cochleae were processed to assess ototoxic effects and to compare normative data for the intact ears.

A baseline ABR was performed to document the hearing thresholds of all right ears, after which a wide perforation of the TM (approximately 75%) was created. This was followed by a second ABR. The right ears then were inoculated with 10/6/ colony forming units of P aeruginosa (Rochester strain). This inoculation was repeated a week later in all animals regardless of their otorrhea or culture status. The animals were observed without any treatment for 4 weeks. During this period, the ears were examined twice a week under the operating microscope, cultures were obtained without suctioning, and findings were recorded. At the end of 4 weeks of drainage, a third ABR was performed on all right ears. Then topical treatment was begun according to group assignment. The medications weredelivered from uniform, color-coded droppers, blinding the study personnel and examiners to group assignment. The pH of the ear drops was 7.5, 5.5, 5.6, 6.6, 5.67, and 6.02 for the groups 1, 2, 3, 4, 5, and 6, respectively. Twice daily for 7 weeks, 3 drops were placed into the right ears. The animals were examined otomicroscopically twice a week, a culture was obtained, and the external ear canals were suctioned. A fourth ABR was performed on all right ears after the fourth week of treatment. The treatment was discontinued after 7 weeks, with continued otoscopic and culture evaluations until the animals were killed. A fifth ABR was performed 1 week after discontinuation of the treatment. All the animals were killed approximately 1 week after the last ABR. On the day the animals were killed, a drug penetration study was performed on selected animals to determine the amount of tobramycin in the perilymph. The animals were killed under heavy anesthesia using vital perfusion with a fixative. The temporal bones were dissected, gross macroscopic findings on the TM and ME were recorded, and biopsy specimens were obtained. The cochleae were perfused with fixative in situ through the round and oval windows and then dissected from the rest of the temporal bone and prepared for cytocochleogram.

SPECIFIC METHODS

Ketamine hydrochloride (10 mg/kg) was used for the anesthesia of the animals for brief procedures such as the otoscopic examinations with culturing and ear drop application. For the ABR, the animals were anesthetized with a mixture of ketamine hydrochloride (13.3 mg/kg), xylazine hydrochloride (2.7 mg/kg), and acepromazine maleate (0.4 mg/kg). The supplement was given as needed using half the initial dose.

Otoscopic examinations were performed with the operating microscope (M703F; Storz Instrument Co, St Louis, Mo) at 16X magnification. Sterile neonatal speculi (Storz Instrument Co) and pediatric disposable speculi (Kleenspec; Welch Allyn, Skaneateles Falls, NY) were used during otomicroscopy. The otoscopic findings were recorded for presence of perforation (perforated, not perforated, or could not evaluate), presence of drainage (yes or no), quantity of drainage (0 indicates no drainage; 1, moist; 2, filling the ME; 3, filling the external auditory canal; and 4, draining out from the external auditory canal), and quality of drainage (serous, mucoid, mucopurulent, or purulent).

A culture was obtained during the otoscopic examination using a calcium alginate fiber-tipped aluminum applicator swab (Fisherbrand Sterile Swabs; Curtin Matheson Scientific, Houston, Tex). The swab was streaked immediately on chocolate agar plates (for isolation of any bacteria present) and Pseudomonas isolation agar (Difco Laboratories, Detroit, Mich) plates (for P aeruginosa). The plates were placed in an incubator at 37 degreesC and read at 24, 48, and 72 hours.

After 4 weeks without treatment, the ears were suctioned (sterile 5F or 3F cannulas; Storz Instrument Co) after

Ciprofloxacin: Use as a Topical Otic Preparation (Article)

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Most common topical otic preparations have been shown to cause sensorineural hearing loss and hair-cell damage in experimental animals. Cirpofloxacin is a relatively new fluoroquinolone with excellent activity against Pseudomonas and methicillin-resistant Staphylococcus aureus. Recent studies have shown oral ciprofloxacin to be effective in the treatment of chronic serous otitis media and malignant external otitis. However, this drug has never been used as a topical otic preparation. Thirty-five albino female guinea pigs were used to investigate the ototoxicity of topical ciprofloxacin hydrocholoride. Bilateral transbullae drug delivery tubes were placed and auditory brain-stem response thresholds were recorded at 20, 16, 8, and 4 kHz before treatment and 21 days after the completion of treatment. Two groups of guinea pigs were used. In group 1 (positive controls), five guinea pigs had 0.1 mL of neomycin sulfate administered in one ear while the opposite (control) ear received 0.1 mL of 0.9% sodium chloride solution; in group 2, 30 guinea pigs received 0.75% ciprofloxacin ophthalmic solution and 0.9% sodium chloride solution in the control ear. All drugs were given twice a day for 7 consecutive days. All results were evaluated with paired, two-tailed t test and Hotelling's \T.sup.2 test, and calculation of power was performed on all nonsignificant results. No significant ototoxic reaction was observed; small increases in hearing thresholds occurred at 4 (5.65 \+ or - 8.25 dB \mean \+ or - SD\) and 8 kHz (3.70 \+ or - 6.63 dB \,ean \+ or - SD\) in the ciprofloxacin-treated ears; however, no significant hair-cell loss was seen. Therefore, the hearing loss appears to be due to middle-ear mucosal changes. The planning and analysis of negative experimental trials is discussed, and a model for testing potentially nonototoxic drugs is presented. (Arch Otolaryngol Head Neck Surg. 1992;118:392-396)

It is estimated that over 1 million myringotomies with insertion of pressure equalization tubes are now performed each year, making this the most common surgical procedure performed in the United States. \1 A relatively common and often frustrating complication of tympanostomy tubes is chronic suppurative otitis media (CSOM), with a reported incidence of 3.6% to 21% in patients with tympanostomy tubes. \2,3 Another even more common problem is otorrhea (aural discharge), which may or may not progress to CSOM. The irreversible tissue damage caused by the most common pathogens in these processes, Pseudomonas aeruginosa and Staphylococcus aureus, often make systemic therapy impractical and ineffective, necessitating the use of topical preparations. \4 Combination topical otic preparations (Coly-Mycin, Cortisporin, Chloromycetin, Garamycin, Otobiotic, Pyocidin Otic, Lazersporin, etc) are used to treat a variety of middle- and external-ear infections. They remain the cornerstone of treatment for many infectious disorders of the ear despite the presence of ototoxic drugs in these drops and convincing evidence of sensorineural hearing loss in animals following their use. \5-18 The major components of these drops include neomycin, polymyxin B, gentamicin, and chloramphenicol, all of which have been shown to be ototoxic on local application and most with systemic administration also. \5-18 While some investigators believe that swelling and inflammation offer a protective factor against the absorption of **drug** through the **round window** membrane, the potential for damage still exists.

Thus, an alternative topical antibiotic preparation with an appropriate antimicrobial spectrum and no risk of ototoxicity would be a welcome and valuable addition to our armamentarium to treat this common problem. /19-21/ Ciprofloxacin hydrochloride is a new fluoroquinolone whose antimicrobial spectrum is excellent against most major pathogens reported in late otorrhea and CSOM with and without cholesteatoma. /1,22-30/ It has shown no signs of systemic ototoxicity. /22,31-33/ Recent studies, although small and uncontrolled, have shown oral ciprofloxacin to be effective in the treatment of CSOM. /23,24/ With its excellent activity against

Pseudomonas, it may also be of value in treating otitis externa, especially in severe cases, such as malignant external otitis. /22-25/ The purpose of this study was to design a method of evaluating possible nonototoxic drugs and to use this to investigate the effects of a topical ciprofloxacin solution on the inner ear. A number of previous investigations have examined the topical ototoxicity of other antibiotics. /4-16,18-21,34/ For our study, six criteria were identified as important to our design: (1) an animal susceptible to ototoxic reaction; (2) multiple dosing of the drug; (3) electrophysiological and histological evaluation; (4) a3- to 4-week waiting period before final evaluation; (5) positive controls to validate the technique; and (6) statistical analysis of the results. Most prior studies have evaluated drugs known or thought to be ototoxic. /4-18/ Since we are searching for a drug lacking ototoxicity, we decided to plan for a "negative trial." Previous reports have documented the frequent failure of prior planning and statistical analysis of negative trials. /19,35/ To minimize the previously reported problems, th present study was designed with the assistance of the Biometrics Consulting Laboratory at the University of North Carolina, Chapel Hill. We devoted particular attention to establishing the power of the study to detect given changes in the inner ear. MATERIALS AND METHODS Experimental Protocol Thirty-five healthy female Sprague-Dawley albino guinea pigs (average weight, 225 g) were anesthetized with 20 mg/kg of intraperitoneal pentobarbital sodium (50 mg/mL) and 30 mg/kg of intramuscular ketamine hydrochloride (100 mg/mL); the ketamine administration was repeated as needed. Through a post-auricular incision, the bulla was identified, a hole was drilled (care was taken not to injure the tympanic annulus or ossicles), and previously prepared drug delivery tubes were placed and secured with cyanoacrylate glue. Body temperature was maintained at 37/degrees/C with a thermostatically controlled heating pad. All procedures were randomized as to side of initial surgery, auditory brain-stem responses (ABRs), and treatment before any procedure. The tympanic membranes were inspected, and initial ABRs (ABR1) were recorded (see "ABR Recording" section). Guinea pigs were inspected for nystagmus and returned to the animal colony. Drug treatment was begun 24 hours after surgery in all guinea pigs. Two groups of guinea pigs were used. In group 1, five guinea pigs had 50 mg/mL of neomycin sulfate (Roxane, Columbus, Ohio) placed in one ear via the drug delivery tube, while the opposite ear received 0.9% sodium chloride solution. In group 2, 30 guinea pigs had 0.75% ciprofloxaxin ophthalmic solution (lot 1884, Alcon Laboratories, Fort Worth, Tex) placed in one ear via the drug delivery tube, and the opposite ear received 0.9% sodium chloride solution. The pH of the ciprofloxacin ophthalmic solution was 4.4 to 4.6, and it contained 0.1% benzalkonium chloride, sodium acetate, and mannitol. Each treatment consisted of 0.1 mL of the assigned drug and was given twice a day (8 AM and 5 PM) for 7 consecutive days. Twenty-one days after completion of drug treatment, all guinea pigs were reanesthetized and ABRs (ABR2) were recorded. After completion of ABRs, the guinea pigs were killed by pentobarbital overdose, and the cochleas were removed and prepared for histological study (see "Histological Evaluation" section). Auditory Brain-Stem Response Recording Auditory brain-stem responses were recorded in a sound-treated room immediately postoperatively and 21 days after treatment. Tone bursts of 4, 8, 16, and 20 kHz (trapezoidal ramp of 1 millisecond, plateau of 3 milliseconds) were administered at a pulse rate of 10 per second from 80 dB sound pressure level (SPL) to threshold in a closed acoustical system composed of a piezoelectric speaker (Motorola, Schaumburg, Ill) coupled to a custom speculum via flexible tubing giving an acoustical delay of 1.13 milliseconds. Sound pressure was monitored at the tympanic membrane level with a probe microphone (Etymotics ER-7C, Elk Grove Village, Ill). The signal was amplified 200 000 times and band-pass filtered 100 to 3000 Hz (Princeton Applied Research PAR113, Princeton, NJ). Five hundred responses for each frequency were processed, stored, and averaged by a signal averaging system (RC Electronics RC-200, Santa Barbara, Calif). Sampling time was 1 microsecond, with an 8.1-millisecond window. Stimulus intensity was decreased in 5-dB steps until no response was detected. Threshold was defined as the intensity at which a response was last observed; all ABR threshold determinations were made by the same observer (R.E.B.). Histological Evaluation Immediately following death, the temporal bones

were removed, and the perilymphatic spaces were perfused with phosphate-buffered 4% glutaraldehyde solution (pH 7.4). The cochleas were then decalcified in 10% edetic acid for 2 to 3 days until adequate for dissection. They were then bisected and all four turns were removed by microdissection, preserving the hook portion of the basal turn. The hair cells were stained with alcian blue and 1% orcine. Sections were mounted in glycerin on slides for examination by bright-field microscopy. Hair cells were counted in 200-/micrometer/ segments beginning at the hook and continuing toward the apex. Results are expressed as a percentage hair-cell loss in each cochlear turn. Data Analyses Interaural differences (IADs), defined as ciprofloxacin or neomycin threshold minus saline threshold, were calculated from ABR1 (IAD1) and ABR2 (IAD2). The change in IAD was calculated by subtracting IAD1 from IAD2. The results were analyzed by a two-tailed, paired t test. The difference in hearing threshold from ABR1 to ABR2 was determined for both the experimental and control ears. This difference was analyzed by a two-tailed, paired t test. Thirteen guinea pigs with the highest posttreatment hearing thresholds in the ciprofloxacin-treated ears were selected for histological evaluation. Histological data were evaluated in a similar manner; the percentage hair-cell loss in each of the four turns was calculated, the saline-treated ear was compared with the ciprofloxacin-treated ear, and the results were analyzed by a two-tailed, paired t test. Mean differences from the four turns were then evaluated with Hotelling's /T.sup.2/ test. Power calculations were performed on both the ABR and histological data, using the following formula: Power = 1 -- Probability |t(df, lambda)|/is less than or equal to/t(alpha=0.975, df), where lambda equals sigma/(/Omega///square root of n/), with sigma being the mean difference scores,}, with /Omega/ as the SD of the difference scores; t(alpha=0.975, n-1) as a standard t value at alpha level 0.975 with df=n-1; and n equals the number of guinea pigs. n-1 and lambda is the mean of the difference scores/(SD of the difference scores/n 1/2). All results are reported as mean/+ or -/SD. RESULTS Auditory Brain-Stem Response Results Group 1 (Neomycin vs Saline).--The mean (/+ or -/SD) change in IAD was 13.93/+ or -/6.23 dB at 20 kHz, 21.35/+ or -/9.55 dB at 16 kHz, 21.56/+ or -/9.65 dB at 8 kHz, and 26.15/+ or -/11.70 dB at 4 kHz. This yielded P values of .003, .007, .015, and .01, respectively. The changes in hearing threshold for the control ears were 4.00/+ or -/1.79 dB at 20 kHz (P=.35), 4.47/+ or -/2.00 dB at 16 kHz (P>.50), 10.68/+ or -/4.78 dB at 8 kHz (P=.50), and 7.35/+ or -/3.29 dB at 4 kHz (P>.50). All calculations were done with n=5; no guinea pigs were excluded (Fig 1). Group 2 (Ciprofloxacin vs Saline).--The mean (/+ or -/SD) IAD at ABR1 (IAD1) was 0.56/+ or -/4.9 dB at 20 kHz, 0.56/+ or -/4.37 dB at 16 kHz, 0.18/+ or -/3.72 dB at 8 kHz, and 0.37/+ or -/4.49 dB at 4 kHz (Fig 2). Changes in IAD were 0.87/+ or -/4.34 dB at 20 kHz (P=.35), 0.65/+ or -/5.77 dB at 16 kHz (P=.5), 3.70/+ or -/6.63 dB at 8 kHz (P=.01), and 5.65/+ or -/8.25 dB at 4 kHz (P<.01). Hearing thresholds from ABR1 to ABR2 improved at 16 kHz for both experimental and control ears (-3.26/+ or -/5.82 dB, P=.01, and -2.61/+ or -/3.86 dB, P<.01, respectively). Otherwise, there were no significant changes in thresholds in the control ears. Hearing thresholds in ciprofloxacin-treated ears were not changed at 20 kHz; they were changed, however, at 8 kHz (3.91/+ or -/7.06 dB, P=.015) and 4 kHz (6.09/+ or -/9.66 dB, P<.01). All calculations were based on n=23. Seven guinea pigs were excluded; three died perioperatively, two suffered stenosis of the external auditory canal, and two had perforations of their tympanic membranes at the time of ABR (Figs 3 and 4). Power calculations were performed on the data from 16 and 20 kHz, and the results are presented in Table 1 (see also Figs 5 and 6). Histological Results The results of group 2 guinea pigs are presented first. Turn 1 showed a mean (/+ or -/SD) loss of 1.14%/+ or -/0.56% in the ciprofloxacin-treated ears, while mean (/+ or -/SD) loss in the saline-treted ears was 1.07%/+ or -/0.37% (P=.55). Turn 2 showed a loss of 1.40%/+ or -/0.59% with ciprofloxacin and 1.19%/+ or -/0.68% with saline (P=.43). Turn 3 had 1.65%/+ or -/0.65% of the ciprofloxacin-treated ears' hair cells missing as compared with 1.29%/+ or -/0.48% of the saline-treated ears' hair cells (P=.11). The losses in turn 4 for ciprofloxacin and saline were 1.55%/+ or -/0.49% and 1.29%/+ or -/0.57%, respectively (P=.17) (Fig 7). The mean differences from all four turns were

compared with Hotelling's /T.sup.2/ test, which resulted in /T.sup.2/=1.473, /5,10/ (P=.29). Power calculations were performed on data from turns 1 through 4, and the results are presented in Table 2. Group 1 guinea pigs showed complete loss of the organ of Corti in all four turns on the side treated with neomycin. The saline-treated control ears showed a loss of 1.00%/+ or -/0.43% in turn 1, 2.10%/+ or -/0.71% in turn 2, 0.70%/+ or -/0.39% in turn 3, and 0.90%/+ or -/0.55% in turn 4. The differences were so large that no t test was performed.

Table 1.--Results of Power Calculations of Possible IADS at 16 and 20 kHz (*)

Change in IAD,dB	Power 16 kHz	20 kHz
0.50	.059	.076
1.00	.122	.184
2.00	.356	.563
3.00	.664	.888
4.00	.888	.988
5.00	.980	...
5.50	.992	...

(*) See text for explanation. IAD indicates interaural differences.

COMMENT Ciprofloxacin is a new fluoroquinolone antibiotic structurally related to nalidixic acid. /22,25,32,36/ This new quinolone has significant activity against P aeruginosa, S aureus (including methicillin-resistant strains), Staphylococcus epidermidis, Enterobacteriac eae, Haemophilus influenzae (including /beta/-lactamase-positive strains), Moraxella (formerly called Branhamella) catarrhalis, and Neisseria species. Ciprofloxacin has only fair activity against Streptococcus species and Enterococcus, and it has poor activity against Bacteroides fragilis and other anaerobic bacteria. /22,25,32,36/ Since the major bacterial isolates from patients with CSOM and late otorrhea include Pseudomonas, S aureus, S epidermidis, and other gram-negative organisms, ciprofloxacin would seem a logical choice for treatment. /1,19-21,26-30,34/ Piccirillo and Parnes, /23/ in a prospective study of 21 patients with chronic ear disease, showed that 95% of the patients completing therapy with oral ciprofloxacin showed either improvement or cure. The hearing loss detected in our study was only

Table 2.--Study Power to Detect Different Percentage Hair-Cell Loss at Each of Four Cochlear Turns (*)

Percentage Hair-Cell Loss	Power Turn 1	Turn 2	Turn 3	Turn 4
0.05	.063	0.38	.041	.045
0.10	.136	.055	.066	.077
0.30	.732	.193	.274	.361
0.50	.990	.444	.618	.760
0.70	.999	.720	.884	.961
0.90	333	.904	.982	.998

(*) See text for explanation.

3.70/+ or -/6.63 and 5.65/+ or -/8.25 dB at 4 and 8 kHz; these frequencies would correspond to the upper portion of turn 1 or the lower aspect of turn 2 in the guinea pig cochlea. Investigations in which ototoxic drugs were applied topically have shown the initial effect to be in the higher frequencies. /4-16/ This appears to be caused by diffusion of the **drug** through the **round window** membrane, which then damages the adjacent hair cells on the basal portion of the basilar membrane. /6-10/ Since there was no hearing loss at 16 or 20 kHz (close to the round window and vestibule), it seems unlikely that diffusion through the round window membrane would explain the effect. Additionally, no significant hair-cell

loss was detected in the upper portion of turn 1 or the lower portion of turn 2 (areas on the basilar membrane corresponding to these frequencies). Although other mechanisms of damage to the cochlea have been reported, such as vascular or lymphatic transfer, it is unlikely that these would explain our guinea pigs' hearing loss, as there was no evidence of hair-cell loss in any areas of the organ of Corti. /7/ The hearing loss can best be explained as a conductive loss secondary to middle-ear mucosal changes. Vernon et al /17/ demonstrated that topical application of propylene glycol caused middle-ear adhesions and a conductive hearing loss. Other investigators have also shown changes in the middle ear, including inflammation, granulation tissue, hemorrhage, mucoid secretion, and osteoneogenesis. /5,10,13,18/ Some of these studies might also have shown small conductive changes had they not been overshadowed by sensorineural losses. Many of the preparations causing these inflammatory changes contained benzalkonium chloride; Parker and James /13/ showed this compound to cause a mucoid secretion and osteoneogenesis when applied to the middle ear. This is also a component of the ciprofloxation solution tested in our study and could possibly be a cause of the hearing loss. Another characteristic of the ciprofloxacin solution is its acidity (pH 4.4 to 4.6). No previous studies have shown middle- or inner-ear damage resulting from acidity itself. Normal saline (pH 2.7) has not been shown to cause mucosal or inner-ear damage on topical application; our controls treated with normal saline also demonstrated no hearing loss. /13/ Our study demonstrated no significant hearing loss at 16 or 30 kHz and only minimal increases in threshold at 4 and 8 kHz. There was also no significant difference in hair-cell loss detected in any of the four cochlear turns. To evaluate the significance of negative results, the /beta/ error and power of the study must be carefully considered. Briefly, there are two types of statistical error, type I and type II. Type I error is the probability of a false-positive result, while a type II error is the probability of a false-negative result. The /alpha/ and /beta/ values represent the probability of type I and type II errors, respectively. When considering negative results, one must address the power of the study. Power calculations are also important in planning these trials; such calculations are used to determine the number of subjects needed to obtain significance in detecting a given change. Simply stated, the power calculation is the probability of an experiment to detect an effect of a given size if that effect is present (power=1-/beta/ error). /35-37/ This study has a greater than 99% chance of detecting a 5-dB difference at 20kHz and a 98% chance of detecting a 5-dB difference at 16kHz at a significance level of P=.05 (Figs 5 and 6). The power of this study to detect a 1.0% to 1.5% difference in hair-cell loss in any cochlear turn at a significance level of P=.05 is 90% to 99% (Table 2). Therefore, it is unlikely that we missed detecting a significant sensorineural hearing loss with electrophysiological evaluations, and this is further reinforced by histological data. The present study showed no significant ototoxicity of 0.75% ciprofloxacin ophthalmic solution when repeated doses were applied to the middle ear of albino guinea pigs. Ciprofloxacin ophthalmic solution may prove to be useful in the treatment of CSOM, late otorrhea, and external otitis; however, further studies are needed before recommending its use in these clinical situations. Future investigations should also include examinations of middle-ear mucosal changes. We believe that further studies of ciprofloxacin and other possible nonototoxic topical otic preparations should be planned and evaluated as negative experimental trials.

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S1        159   AU='ARENBERG IRVING K' OR AU='ARENBERG IK' OR AU='ARENBERG
                I.K.'
S2          5   AU='ARENBERG, I. K.':AU='ARENBERG, I.K.'
S3        164   S1 OR S2
S4          4   S3 AND ROUND(2N)WINDOW?
S5          1   AU='ARENBERG MICHAEL H'
S6          4   AU='LEMKE CHRISTINA':AU='LEMKE CHRISTINE'
S7          2   AU='LEMKE, CHRISTINA'
S8          1   AU='BERGLUND JOHN'
S9          8   S5:S8
S10         8   RD (unique items)
S11         1   S10 AND ROUND(2N)WINDOW?
?show files
File 155:MEDLINE(R) 1966-2002/May W2
File 144:Pascal 1973-2002/May W3
         (c) 2002 INIST/CNRS
File   5:Biosis Previews(R) 1969-2002/May W2
         (c) 2002 BIOSIS
File   6:NTIS 1964-2002/Jun W1
         (c) 2002 NTIS, Intl Cpyrght All Rights Res
File   2:INSPEC 1969-2002/May W3
         (c) 2002 Institution of Electrical Engineers
File   8:Ei Compendex(R) 1970-2002/May W3
         (c) 2002 Engineering Info. Inc.
File  99:Wilson Appl. Sci & Tech Abs 1983-2002/Apr
         (c) 2002 The HW Wilson Co.
File 238:Abs. in New Tech & Eng. 1981-2002/May
         (c) 2002 Reed-Elsevier (UK) Ltd.
File  65:Inside Conferences 1993-2002/May W3
         (c) 2002 BLDSC all rts. reserv.
File  77:Conference Papers Index 1973-2002/Mar
         (c) 2002 Cambridge Sci Abs
File  73:EMBASE 1974-2002/May W2
         (c) 2002 Elsevier Science B.V.
File  34:SciSearch(R) Cited Ref Sci 1990-2002/May W3
         (c) 2002 Inst for Sci Info
File 434:SciSearch(R) Cited Ref Sci 1974-1989/Dec
         (c) 1998 Inst for Sci Info
File  94:JICST-EPlus 1985-2002/Mar W5
         (c)2002 Japan Science and Tech Corp(JST)
File  35:Dissertation Abs Online 1861-2002/Apr
         (c) 2002 ProQuest Info&Learning
?
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?ds

Set	Items	Description
S1	160	ROUND()WINDOW? OR RWM
S2	53043	(CONTROL? OR DELAY? OR SUSTAIN?)(3N)(DELIVER? OR RELEASE? OR TARGET?)
S3	571544	DRUG? OR MEDICATION? OR MEDICINE? OR ANTIBIOTIC? OR DOSAGE? OR DOSE? OR DROPS? OR MEDICINAL? OR PHARMACEUTIC? OR REMEDY OR REMEDIES OR MEDICINAL? OR MEDICANT?
S4	11	S1 (5N)2
S5	7	S1 AND S3
S6	2	S1 AND S2 AND S3
S7	1	S1 (5N) S3
S8	6	AU='ARENBERG I K'

?show files
File 350:Derwent WPIX 1963-2001/UD,UM &UP=200232
(c) 2002 Thomson Derwent
File 344:CHINESE PATENTS ABS APR 1985-2002/APR
(c) 2002 EUROPEAN PATENT OFFICE
File 347:JAPIO Oct/1976-2001/Dec(Updated 020503)
(c) 2002 JPO & JAPIO
File 371:French Patents 1961-2002/BOPI 200209
(c) 2002 INPI. All rts. reserv.

8/3,AB/1 **(Item 1 from file: 350)**
DIALOG(R)File 350:Derwent WPIX

013293165
WPI Acc No: 2000-465100/200040
XRAM Acc No: C00-139926
XRPX Acc No: N00-347179

Delivery of therapeutic agents into inner ear comprising placing drug delivery device containing sustained release therapeutic agent into round window niche of subject, where agent contacts window membrane and passes into inner ear

Patent Assignee: DURECT CORP (DURE-N)
Inventor: **ARENBERG I K** ; ARENBERG M H; BERGLUND J A; LEMKE C; THEEUWES F
Number of Countries: 091 Number of Patents: 003
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
WO 200033775	A1	20000615	WO 99US28716	A	19991203	200040	B
AU 200021646	A	20000626	AU 200021646	A	19991203	200045	
EP 1133269	A1	20010919	EP 99965987	A	19991203	200155	
			WO 99US28716	A	19991203		

Priority Applications (No Type Date): US 98205251 A 19981204
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
WO 200033775	A1	E	62	A61F-011/00	

Designated States (National): AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
Designated States (Regional): AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW

AU 200021646	A		A61F-011/00	Based on patent WO 200033775
EP 1133269	A1	E	A61F-011/00	Based on patent WO 200033775

Designated States (Regional): AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI

Abstract (Basic): WO 200033775 A1
Abstract (Basic):

NOVELTY - A method for delivery of therapeutic agents into the inner ear of a subject over time comprises placing at least a portion of a drug delivery unit into a round window niche of the subject, where the drug delivery unit comprises at least one synthetic carrier media material, at least one cross-linked carrier media material or at least one sustained release synthetic carrier medium, and at least one therapeutic agent, and the therapeutic agent contacts and passes through the round window membrane and enters the inner ear.

ACTIVITY - Auditory.

USE - For delivery of drugs into the inner ear (claimed), particularly in treatment of endolymphatic hydrops, endolymphatic hypertension, perilymphatic hypertension, perilymphatic hydrops, perilymphatic fistula, intracochlear fistula, Meniere's disease, tinnitus, vertigo, hearing loss related to hair cell or ganglion cell damage or malfunction and ear membrane ruptures.

ADVANTAGE - The process allows controlled drug delivery with easy termination of therapy if required.

DESCRIPTION OF DRAWING(S) - The figure shows the schematic cross-sectional view of the drug delivery unit positioned within the round window niche.

Ear canal (5)
Drug delivery unit (10)
Soft or semi-soft mass (12)
Controlled release carrier material (14)
Therapeutic agent (16)
Ear (40)
Round window niche (42)

Inner ear (44)
Round window membrane (46)
Middle ear (50)
Interior side wall (54)
Main opening (56)
Tympanic membrane (60) and
Incision (62).
pp; 62 DwgNo 2/8

8/3,AB/2 (Item 2 from file: 350)
DIALOG(R)File 350:Derwent WPIX

012989389
WPI Acc No: 2000-161242/200014
XRAM Acc No: C00-050509
XRPX Acc No: N00-120259

Apparatus for treating and/or diagnosing conditions of inner ear has conduit having internal passageway(s) and connected to inflatable bladder for inflating and engaging internal ear cavity

Patent Assignee: DURECT CORP (DURE-N)
Inventor: **ARENBERG I K** ; ARENBERG M H
Number of Countries: 085 Number of Patents: 003
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
WO 200004854	A1	20000203	WO 99US15683	A	19990712	200014	B
AU 9950962	A	20000214	AU 9950962	A	19990712	200029	
EP 1098614	A1	20010516	EP 99935496	A	19990712	200128	
			WO 99US15683	A	19990712		

Priority Applications (No Type Date): US 98121460 A 19980723
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
WO 200004854	A1	E	10	A61F-011/00	
AU 9950962	A			A61F-011/00	Based on patent WO 200004854
EP 1098614	A1	E		A61F-011/00	Based on patent WO 200004854

WO 200004854 A1
Designated States (National): AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
Designated States (Regional): AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
EP 1098614 A1
Designated States (Regional): AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI

Abstract (Basic): WO 200004854 A1
Abstract (Basic):

NOVELTY - The medical treatment apparatus has an inflatable bladder (46) connected to a conduit (12) having internal passageways (62,134). In use, the bladder is placed within and inflated to engage the internal cavity of the ear. An elongate conductive member (102) is operatively connected to a conduit.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a method for moving fluid materials through the round window niche and round window membrane.

USE - For treating and/or diagnosing conditions of the inner ear.

ADVANTAGE - The fluids can be efficiently delivered to or removed from the inner ear.

DESCRIPTION OF DRAWING(S) - Figure of a schematic view of the fluid transfer and diagnostic apparatus.

Conduit (12)
Inflatable bladder (46)
Internal passageways (62,134)
Conductive member (102)
pp; 10 DwgNo 8/9

8/3,AB/3 (Item 3 from file: 350)
DIALOG(R)File 350:Derwent WPIX

012299399
WPI Acc No: 1999-105505/199909
XRAM Acc No: C99-031349
XRPX Acc No: N99-076204

Apparatus for delivering therapeutic agents to or analysing conditions of inner ear - has single fluid transfer conduit or separate fluid extraction and fluid delivery extending through cover that seals over main opening of round window niche of inner ear

Patent Assignee: DURECT CORP (DURE-N); INTRAEAR INC (INTR-N)
Inventor: **ARENBERG I K** ; ARENBERG M H
Number of Countries: 083 Number of Patents: 005
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
WO 9856434	A1	19981217	WO 98US12194	A	19980611	199909	B
AU 9880680	A	19981230	AU 9880680	A	19980611	199920	
EP 989868	A1	20000405	EP 98929016	A	19980611	200021	
			WO 98US12194	A	19980611		
US 6045528	A	20000404	US 97874208	A	19970613	200024	
AU 737470	B	20010823	AU 9880680	A	19980611	200154	

Priority Applications (No Type Date): US 97874208 A 19970613
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
WO 9856434	A1	E	129	A61M-001/00	
Designated States (National): AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM GW HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW					
Designated States (Regional): AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW					
AU 9880680	A				Based on patent WO 9856434
EP 989868	A1	E		A61M-001/00	Based on patent WO 9856434
Designated States (Regional): AT BE CH DE DK ES FI FR GB GR IE IT LI LU NL PT SE					
US 6045528	A			A61M-001/00	
AU 737470	B			A61M-001/00	Previous Publ. patent AU 9880680 Based on patent WO 9856434

Abstract (Basic): WO 9856434 A

Medical treatment apparatus has either a single fluid transfer conduit or separate fluid extraction and fluid delivery conduits (16, 50), each connected to and extending through a cover (12) using cover seals over a main opening of the round window niche of the inner ear. The cover is compressible so, when placed in the niche it expands and forms a seal. Also claimed are methods of transferring, delivering or collecting fluid to and from the inner ear using an apparatus as above.

USE - An apparatus for delivering therapeutic agents to or analysing conditions of the inner ear is provided.

ADVANTAGE - The fluid is supplied and/or removed locally, rapidly and controllably via the round window membrane

Dwg.1/10

8/3,AB/4 (Item 4 from file: 350)
DIALOG(R)File 350:Derwent WPIX

010682243
WPI Acc No: 1996-179198/199618
XRAM Acc No: C96-056433

XRPX Acc No: N96-150692

Manufacture of medical implant, esp. for otological use - uses collagen container filled with granules and activator causing granules to form rigid member

Patent Assignee: WILDFLOWER COMMUNICATIONS INC (WILD-N)
Inventor: **ARENBERG I K**
Number of Countries: 063 Number of Patents: 003
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
US 5501706	A	19960326	US 94346012	A	19941129	199618	B
WO 9734547	A1	19970925	WO 96US3895	A	19960322	199744	N
AU 9655255	A	19971010	AU 9655255	A	19960322	199806	N
			WO 96US3895	A	19960322		

Priority Applications (No Type Date): US 94346012 A 19941129; WO 96US3895 A 19960322; AU 9655255 A 19960322
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
US 5501706	A		20	A61F-002/28	
WO 9734547	A1	E	53	A61F-002/28	

Designated States (National): AM AT AU BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU JP KE KG KP KR KZ LK LR LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SI SK TJ TT UA UZ VN
Designated States (Regional): AT BE CH DE DK ES FI FR GB GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG

AU 9655255	A		A61F-002/28	Based on patent WO 9734547

Abstract (Basic): US 5501706 A

Medical implant (10) comprises a collagen container (14) filled with granular implant material. An activator material is supplied to the implant material where it sticks the individual granules together to form a temporarily pliable mixture which ultimately solidifies to produce a solid mass.

USE - The implant is esp. useful for otological procedures, e.g. ear canal wall reconstruction, and the filling of open zones caused by tumour removal and bone loss due to osteomyelitis, mastoidectomy, etc.. It is also useful in a wide variety of neurosurgical, dental, orthopaedic and plastic surgery/reconstructive procedures.

ADVANTAGE - The implant is readily manufactured using a minimal number of components and process steps.

Dwg.3/6

8/3,AB/5 (Item 5 from file: 350)

DIALOG(R)File 350:Derwent WPIX

010304614
WPI Acc No: 1995-205874/199527
XRPX Acc No: N95-161292

Diagnosing-treatment endoscope for medical applications - has laser light supply device for delivering laser light to probe, whose medial portion includes first light transmission device for receiving laser light from laser light source device

Patent Assignee: WILDFLOWER COMMUNICATIONS INC (WILD-N)
Inventor: **ARENBERG I K** ; FLOCK S T; WANER M
Number of Countries: 001 Number of Patents: 001
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
US 5419312	A	19950530	US 9350555	A	19930420	199527	B

Priority Applications (No Type Date): US 9350555 A 19930420
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
US 5419312	A		21	A61B-001/06	

Abstract (Basic): US 5419312 A

The appts includes a flexible probe having a medial portion, first and second ends, the first end of the probe being sized for placement within the body cavity. A laser light supply device is operatively connected to the probe for delivering laser light to the probe.

A first light transmission device is positioned within the medial portion of the probe for receiving the laser light from the laser light supply device. The latter is operatively connected to the laser light supply device in order to receive the laser light from it. The laser light is delivered by the first light transmission device to the body cavity when the first end of the probe is positioned.

USE/ADVANTAGE - To perform endoscopic observation of body cavities. Capable for insertion within relative small body cavities such as inner ear, while producing images for observation, with provision for delivering laser light for treatment purposes.

Dwg.1/8

8/3,AB/6 (Item 6 from file: 350)

DIALOG(R)File 350:Derwent WPIX

010268751

WPI Acc No: 1995-170006/199522

XRPX Acc No: N95-133302

Multi function inner ear treatment and diagnosis probe - has porous reservoir for medicines connected to tubular stem with electrical conductor for ECoG potentials

Patent Assignee: INNER EAR MEDICAL DELIVERY SYSTEMS INC (INNE-N)

Inventor: **ARENBERG I K**

Number of Countries: 028 Number of Patents: 007

Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
WO 9510984	A1	19950427	WO 94US11846	A	19941017	199522	B
US 5421818	A	19950606	US 93138827	A	19931018	199528	
AU 9480817	A	19950508	AU 9480817	A	19941017	199533	
US 5474529	A	19951212	US 93138827	A	19931018	199604	
			US 95426215	A	19950421		
US 5476446	A	19951219	US 93138827	A	19931018	199605	
			US 95426190	A	19950421		
EP 724408	A1	19960807	EP 94931900	A	19941017	199636	
			WO 94US11846	A	19941017		
AU 682908	B	19971023	AU 9480817	A	19941017	199750	

Priority Applications (No Type Date): US 93138827 A 19931018; US 95426215 A 19950421; US 95426190 A 19950421

Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
WO 9510984	A1	E	110	A61B-017/36	
Designated States (National): AU CA CN CZ FI JP KR NO NZ RU					
Designated States (Regional): AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE					
US 5421818	A		28	A61M-025/00	
AU 9480817	A			A61B-017/36	Based on patent WO 9510984
US 5474529	A		27	A61M-025/00	Div ex application US 93138827 Div ex patent US 5421818
US 5476446	A		27	A61M-025/00	Div ex application US 93138827 Div ex patent US 5421818
EP 724408	A1	E	1	A61B-017/36	Based on patent WO 9510984
Designated States (Regional): AT BE CH DE DK ES FR GB IE IT LI LU NL PT SE					
AU 682908	B			A61F-011/00	Previous Publ. patent AU 9480817 Based on patent WO 9510984

Abstract (Basic): WO 9510984 A

The device (10) delivers therapeutic agents to the middle and inner

ear. It has a tubular stem (14) joined to a medicine reservoir (30), permitting fluid transfer through its walls. The fluid, or medicine, may be transferred by multiple pores (46), or via a semi-permeable membrane, in contact with middle-inner ear tissue. The stem passage may include a valve.

Part of the device may be radiopaque, visible to X rays. An electrical conductor (70), fixed to the device, may carry potentials in and out of the inner ear. The conductor may have a spherical end (86), for electrocochleography. The reservoir may have a double wall and the stem may have an inflatable section, pressurising the reservoir.

USE/ADVANTAGE - Therapeutically testing, treating and/or analysing conditions of ear by delivering medicaments, withdrawing fluids, changing fluid temperature, pressure and volume, in inner ear.

Dwg.1/15

Abstract (Equivalent): US 5476446 A

A treatment apparatus for delivering therapeutic agents into the inner ear of a human subject comprising:

a reservoir portion comprising an exterior wall and an internal cavity in it surrounded by the wall;

a tubular first stem portion comprising an open first end, a second end, and a passageway extending continuously through the first stem portion, the second end of the first stem portion being connected to the reservoir portion so that the passageway through the first stem portion is in fluid communication with the internal cavity in the reservoir portion; and

a tubular second stem portion comprising an open first end, a second end, and a passageway extending continuously through the second stem portion, the second end of the second stem portion being connected to the reservoir portion so that the passageway through the second stem portion is in fluid communication with the internal cavity in the reservoir portion.

Dwg.11/15

US 5474529 A

The probe comprises a first reservoir with an exterior wall and an internal cavity surrounded by wall, a tubular first stem portion comprising a first and second end, and a passageway extending continuously through first and second end of said first stem portion being connected to said first reservoir portion so that said passageway through said first stem portion is in fluid communication with said internal cavity in said first reservoir portion, a tubular second stem portion comprising a first and second end, and a passageway extending continuously through said second stem portion, said second end of said second stem portion being connected to said first reservoir portion so that said passageway through said second stem portion is in fluid communication with said internal cavity in said first reservoir portion.

A second reservoir portion comprising an exterior wall and an internal cavity therein surrounded by said wall of said second reservoir portion, said first end of said first stem portion being connected to said second reservoir portion so that said passageway through said first stem portion is in fluid communication with said internal cavity in said second reservoir portion and at least one tubular additional stem portion.

Dwg.12/15

US 5421818 A

The apparatus (10) includes the reservoir (30) which consists of front, rear and blunt end portions. The blunt end portion consists of a continuous, uninterrupted exterior surface with the reservoir also having an exterior wall surrounding an internal cavity (38). Fluids pass through the porous wall of the reservoir which has an opening with a semi-permeable membrane across it. The tubular stem (14) has an open first end (20), a second end (22) connected to the reservoir and a passageway (24) which extends through the stem.

The passageway communicates fluids with the internal cavity in the reservoir and a valve is located within the passageway. At least part of the apparatus is radiopaque and visible when X-rays are applied. An

elongated conductor attached to the reservoir wall transmits electrical potentials into and out of the inner ear. The medicine is delivered through the external auditory canal of the ear and into the round window membrane within the middle ear where it diffuses into the inner ear.

ADVANTAGE - Controlled, repeatable and uniform delivery to selected ear tissue regions. Compact size permits insertion using minimally-invasive microsurgery. Easily supplied with medicine while inserted in ear.

Dwg.2/15

?

?t s4/9/1,2,3

4/9/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12690930 BIOSIS NO.: 200000444432
Inner ear fluid transfer and diagnostic system.
AUTHOR: **Arenberg Irving K** (a); Arenberg Michael H
AUTHOR ADDRESS: (a)Englewood, CO**USA
JOURNAL: Official Gazette of the United States Patent and Trademark Office Patents 1233 (1):pNo pagination Apr. 4, 2000
MEDIUM: e-file
PATENT NUMBER: US 6045528 PATENT DATE GRANTED: April 04, 2000 20000404
PATENT ASSIGNEE: IntraEar, Inc., Greenwood Village, CO, USA
PATENT COUNTRY: USA
ISSN: 0098-1133
DOCUMENT TYPE: Patent
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: An apparatus for transferring fluids into and out of the inner ear through the **round window** membrane. The apparatus includes a cover member sized for placement over the **round window** niche. Fluid delivery and fluid extraction conduits are provided which are operatively connected to the cover member so that fluids can pass therethrough. The cover member is positioned over the niche to create a fluid-recieving zone between the cover member and the **round window** membrane. As a result, fluids can be delivered into or withdrawn from the zone. Alternatively, a single conduit may be used for fluid delivery and extraction. Another variation uses a compressible cover member positioned within the **round window** niche to form a fluid-receiving zone between the cover member and the **round window** membrane. The same type of conduit system described above is attached to the compressible cover member.

DESCRIPTORS:
MAJOR CONCEPTS: Equipment, Apparatus, Devices and Instrumentation; Otolaryngology (Human Medicine, Medical Sciences); Methods and Techniques
BIOSYSTEMATIC NAMES: Hominidae--Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGANISMS: human (Hominidae)
ORGANISMS: PARTS ETC: inner ear--sensory system
BIOSYSTEMATIC CLASSIFICATION (SUPER TAXA): Animals; Chordates; Humans; Mammals; Primates; Vertebrates
MISCELLANEOUS TERMS: fluid transfer; medical diagnostics
BIOSYSTEMATIC CODES:
86215 Hominidae

4/9/2 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

10761076 EMBASE No: 2000240902
Round - Window -**Microcatheter administered microdose of gentamycin: An alternative in treatment of tinnitus associated with Meniere's disease**
ROUND - WINDOW -MIKROKATHETER-ASSISTIERTE MIKRODOSIERUNG VON GENTAMYCIN: ALTERNATIVE IN DER BEHANDLUNG DES TINNITUS BEI PATIENTEN MIT MORBUS MENIERE
Marks S.; **Arenberg I.K.** ; Hoffer M.E.
Dr. S. Marks, Sassengarten 7, 29223 Celle Germany
Laryngo- Rhino- Otologie (LARYNGO- RHINO- OTOL.) (Germany) 2000, 79/6 (327-331)
CODEN: LROTE ISSN: 0935-8943
DOCUMENT TYPE: Journal; Article

LANGUAGE: GERMAN SUMMARY LANGUAGE: ENGLISH; GERMAN
NUMBER OF REFERENCES: 23

Background: In this study, we review the results of Meniere's disease treatment using microdose gentamycin delivered directly to the **round window** using a new microcatheter system. Patients and Methods: 11 patients were treated by 1.25 mg gentamycin on the 3rd and 7th day after insertion of the new microcatheter at the niche of the **round window** membrane, while a second group of 7 patients was treated by a gentamycin dosage of 1 mul/h continuously applicated by a minipump over a period of 10 days. Electrocochleography was derived by an integrated electrode and the microcatheter was removed after 10 days. The results were analyzed with a follow-up ranging from 6 to 12 months. Results: In 15 of 18 patients (83%) tinnitus was improved significantly throughout the follow-up period. Vertigo was eliminated in all patients, and pressure was relieved in 17 of 18 (94%). Conclusions: These preliminary data suggest that gentamycin delivered by the **Round - Window** -Microcatheter is a safe and effective treatment for the reduction of tinnitus, vertigo, and pressure associated with Meniere's disease.

DRUG DESCRIPTORS:
*gentamicin--clinical trial--ct; *gentamicin--drug dose--do; *gentamicin --drug therapy--dt; *gentamicin--pharmacology--pd; *gentamicin --intratympanic drug administration--ty
MEDICAL DESCRIPTORS:
*Meniere disease; *tinnitus--drug therapy--dt; *cochlea fenestra catheterization; dose response; electrocochleography; vertigo; middle ear pressure; drug safety; human; clinical article; clinical trial; article; priority journal
CAS REGISTRY NO.: 1392-48-9, 1403-66-3, 1405-41-0 (gentamicin)
SECTION HEADINGS:
011 Otorhinolaryngology
037 Drug Literature Index

4/9/3 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

08803927 Genuine Article#: 330NR Number of References: 23
Title: Round - Window **-Microcatheter administered microdose of gentamycin: An alternative in treatment of tinnitus associated with Meniere's disease.**
Author(s): Marks S (REPRINT) ; **Arenberg IK** ; Hoffer ME
Corporate Source: SASSENGARTEN 7,/D-29223 CELLE//GERMANY/ (REPRINT); PROSPER MENIERE SOC,/ENGLEWOOD//CO/
Journal: LARYNGO-RHINO-OTOLOGIE, 2000, V79, N6 (JUN), P327-331
ISSN: 1615-0007 Publication date: 20000600
Publisher: GEORG THIEME VERLAG, RUDIGERSTR 14, D-70469 STUTTGART, GERMANY
Language: German Document Type: ARTICLE
Geographic Location: GERMANY; USA
Subfile: CC CLIN--Current Contents, Clinical Medicine
Journal Subject Category: OTORHINOLARYNGOLOGY
Abstract: In this study, we review the results of Meniere's disease treatment using microdose gentamycin delivered directly to the **round window** using a new microcatheter system. Patients and Methods: 11 patients were treated by 1.25 mg gentamycin on the 3rd and 7th day after insertion of the new microcatheter at the niche of the **round window** membrane, while a second group of 7 patients was treated by a gentamycin dosage of 1 mu l/h continously applicated by a minipump over a period of 10 days. Electrocochleography was derived by an integrated electrode and the microcatheter was removed after 10 days. The results were analysed with a follow-up ranging from 6 to 12 months. Results: In 15 of 18 patients (83%) tinnitus was improved significantly throughout the follow-up period. Vertigo was eliminated in all patients; and pressure was relieved in 17 of 18 (94%). Conclusions: These preliminary

data suggest that gentamycin delivered by the **Round - Window** -Microcatheter is a safe and effective treatment for the reduction of tinnitus, vertigo, and pressure associated with Meniere's disease.

Descriptors--Author Keywords: Morbus Meniere ; tinnitus ; gentamycin therapy ; **Round - Window** -Microcatheter

Identifiers--KeyWord Plus(R): INTRATYMPANIC GENTAMICIN; AMINOGLYCOSIDES; THERAPY

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> d l9 bib ab 1

L9 ANSWER 1 OF 6 WPIX (C) 2002 THOMSON DERWENT
AN 1997-502180 [46] WPIX
DNN N1997-418661 DNC C1997-159551
TI Administering topical, anaesthetic or sterilising fluids to ear drum or canal, particularly in young children - using earplug with flanges for engaging tragus and concha respectively and through conduit for administering fluids.
DC B07 P34 S05
IN DONALDSON, J; DONALDSON, K
PA (DONA-I) DONALDSON J; (DONA-I) DONALDSON K
CYC 19
PI US 5674196 A 19971007 (199746)* 9p <--
WO 9917825 A1 19990415 (199922)# EN
RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: CA
ADT US 5674196 A US 1996-583342 19960105; WO 9917825 A1 WO 1997-US17957 19971006
PRAI US 1996-583342 19960105; WO 1997-US17957 19971006
AB US 5674196 A UPAB: 19971119
An earplug has anterior and posterior flanges (14, 16) for engaging the tragus and concha respectively to hold the earplug in place so it substantially seals the ear canal. A conduit (40) for administering fluid to the ear canal extends through the earplug. In different aspects: (1) The earplug has a peripheral groove (33) for accommodating a flange collar (22) that interconnects the flanges. The collar is attached to the earplug; and (2) An obturator engages the conduit after the fluid has been administered and has an electrode for performing an iontophoretic process.
USE - The earplug is used for administering topical, anaesthetic or sterilising fluids to the eardrum or ear canal, particularly young children (claimed).
Dwg.1/4

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L1 ANSWER 1 OF 1 DPCI (C) 2002 THOMSON DERWENT
AN 1995-170006 [22] DPCI
DNN N1995-133302
TI Multi function inner ear treatment and diagnosis probe - has porous reservoir for medicines connected to tubular stem with electrical conductor for ECoG potentials.
DC P31 P34 S05
IN ARENBERG, I K
PA (INNE-N) INNER EAR MEDICAL DELIVERY SYSTEMS INC
CYC 28
PI WO 9510984 A1 19950427 (199522)* EN 110p A61B017-36
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE
W: AU CA CN CZ FI JP KR NO NZ RU
US 5421818 A 19950606 (199528) 28p A61M025-00 <--
AU 9480817 A 19950508 (199533) A61B017-36
US 5474529 A 19951212 (199604) 27p A61M025-00
US 5476446 A 19951219 (199605) 27p A61M025-00
EP 724408 A1 19960807 (199636) EN 1p A61B017-36
R: AT BE CH DE DK ES FR GB IE IT LI LU NL PT SE
AU 682908 B 19971023 (199750) A61F011-00
ADT WO 9510984 A1 WO 1994-US11846 19941017; US 5421818 A US 1993-138827 19931018; AU 9480817 A AU 1994-80817 19941017; US 5474529 A Div ex US 1993-138827 19931018, US 1995-426215 19950421; US 5476446 A Div ex US 1993-138827 19931018, US 1995-426190 19950421; EP 724408 A1 EP 1994-931900
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FDT AU 9480817 A Based on WO 9510984; US 5474529 A Div ex US 5421818; US 5476446 A Div ex US 5421818; EP 724408 A1 Based on WO 9510984; AU 682908 B
Previous Publ. AU 9480817, Based on WO 9510984
PRAI US 1993-138827 19931018; US 1995-426215 19950421; US 1995-426190 19950421
IC ICM A61B017-36; A61F011-00; A61M025-00
FS EPI GMPI

EXF EXAMINER'S FIELD OF SEARCH UPE: 19960618

NCL WO 9510984 A1 19950427
128/024.000AA; 128/DIG.120; 604/103; 604/020; 604/021; 604/052; 604/053;
604/892.100; 604/096
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604/892.100; 604/096
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604/892.100; 604/096
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128/024.000AA; 128/DIG.120; 604/103; 604/020; 604/021; 604/052; 604/053;
604/892.100; 604/096

CTCS CITATION COUNTERS

PNC.DI	10	Cited Patents Count (by inventor)
PNC.DX	25	Cited Patents Count (by examiner)
IAC.DI	1	Cited Issuing Authority Count (by inventor)
IAC.DX	3	Cited Issuing Authority Count (by examiner)
PNC.GI	0	Citing Patents Count (by inventor)
PNC.GX	15	Citing Patents Count (by examiner)
IAC.GI	0	Citing Issuing Authority Count (by inventor)
IAC.GX	2	Citing Issuing Authority Count (by examiner)
CRC.I	10	Cited Literature References Count (by inventor)
CRC.X	12	Cited Literature References Count (by examiner)

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	IN: HAERR, R H	
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	IN: NEWKIRK, J B	
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	PA: (ALZA) ALZA CORP	
	IN: ECKENHOFF, J B; GEERKE, J H; LANDRAU, F A	
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IN: JACOBSEN, S C; STENEHJEM, J C; STEPHEN, R L
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IN: BECK, J; JACOBSEN, S C; PETELENZ, T J; STEPHEN, R L
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		IN: ARENBERG, I K; ARENBURG, I K	
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		IN: BUSEY, H W; COMBS, J T; UKRAINCIK, K	

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